Synthesis of novel quinolines, pyrrolo[2,3-*b*]indoles, and 1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-diones via palladium-catalyzed cross-coupling reactions

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Declaration

Hereby I declare that this thesis has been written without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of this thesis other than those indicated in the thesis itself.

Erklärung

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Maksym Cherevatenko

August 2017, Rostock

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Abstract

The present thesis is mainly dedicated to the study of the synthesis of quinolines, pyrolo[2,3-*b*]indoles and 1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-diones via palladium-catalyzed cross-coupling reactions. This includes arylation of quinolines via Suzuki-Miyaura and alkynylation of 4-trifluoromethylquinolines via Sonogashira reaction. Consequent synthesis of a wide range of fused pyridines and their further modifications were successfully performed. A number of pyrolo[2,3-*b*]indoles and pyrimido[4,5-b]indole-2,4(3*H*,9*H*)-diones were synthesized with the usage of Buchwald-Hartwig reaction. Certain compounds showed significant activity as alkaline phosphatase inhibitors.

Kurzbeschreibung

Die vorliegende Arbeit beschäftigt sich mit der Synthese von Chinolinen, Pyrolo[2,3-*b*]indolen und 1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dionen durch Palladium-katalysierte Kreuzkupplungsreaktionen. Sie beinhaltet Arylierungen von Chinolinen mittels Suzuki-Miyaura Reaktion und Alkinylierung von 4-Trifluoromethylchinolinen mittels Sonogashira Reaktion. Die Synthese eines breiten Spektrums an kondensierten Pyridinen und deren weiteren Modifikationen wurde erfolgreich durchgeführt. Außerdem wurden verschiedene Pyrolo[2,3-*b*]indole und Pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione durch Buchwald-Hartwig Reaktion hergestellt. Einige der hergestellten Verbindungen zeigten eine signifikante Aktivität als Inhibitoren der alkalischen Phosphatase.

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Introduction

1.1 Role of palladium in cross-coupling reactions

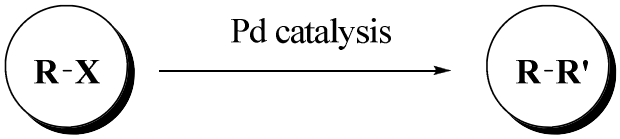
Nowadays chemistry is one of the most intensive and industrially extensive nature sciences spanning countless applications in the syntheses of natural products, polymers, agrochemicals, and pharmaceuticals. The number of new compounds every year extends in exponential growth. Organic synthesis with its long and outstanding history plays an important and influential role and one of the high developing research fields among them now is the chemistry of transition metals. Palladium is one of the most widely used precious metal in organic synthesis and especially in cross-couplings, which are based mostly on palladium, used as effective tools in the construction of a variety of complex molecules.

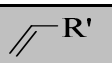
There is an impressive list of a chemical transformation that can be conducted by using transition metal catalysis specifically that features this metal. Among them are a number of well-known name reactions, including the Negishi, Suzuki, Stille, Sonogashira, and Heck cross-couplings (**Table 1.1**). More importantly, palladium is an integral part of numerous hydrogenation and carbonylation reactions, the formation of carbon-carbon bonds in the synthesis of natural products, pharmaceuticals, and other biologically important compounds.

Main advantages of palladium-based methods often proceed under mild conditions affording excellent stereo-, regio-, and chemoselectivity of reactions and exceptionally high yields. This influence of palladium-catalyzed reactions was recognized by scientific world in 2010 by awarding the Nobel Prize to Richard Heck, Akira Suzuki, and Ei-ichi Negishi.[1]

There is a wide range of methods available to construct aromatic heterocycles. Nevertheless, many of these rely upon relatively involved multistep processes, especially for the assembly of highly substituted products. In addition, these can sometimes suffer from harsh reaction conditions, or display limited product diversity.

Table 1.1 Short historical overview of palladium-catalyzed reactions.



Reaction	Reagent	Year of discovery[2–13]
Kumada	R'-MgX	1972
Heck		1972
Sonogashira		1975
Negishi	R'-ZnX	1977
Stille	R'-SiR_3''	1978
Suzuki-Miyaura	R'-$B(OH)_2$	1979
Hyiama	R'-SiR_3''	1988
Buchwald-Hartwig Amination	R'-NH_2	1994 (first examples in 1983 by Migita *et al.*)

The variety of reactions that can be catalyzed together with the range of functional groups tolerated and mild reaction conditions made palladium-catalyzed cross-coupling reaction an ultimate tool in constructing complicated organic molecules. There are two main advantages of palladium in C–C bond-forming reactions:

- ability in the transmetallation reaction of many types of organometallic reagents;
- high activity in addition reactions.

Transition metal-catalyzed reactions proceed through multiple elementary steps and their mechanisms are often complicated. A simplified mechanism for these transformations (shown below **Figure 1**) typically initiates with oxidative addition of the organic halide (or pseudohalide) to a Pd(0) complex to afford intermediate **I**. The

organopalladium halide complex **I** can then undergo transmetalation with the main-group coupling partner (M = Mg, Zn, Si, B, etc.) to afford the diorganopalladium species **II**. Carbon-carbon bond-forming reductive elimination from **II** affords the desired cross-coupling product **III** and regenerates the Pd catalyst. Unfortunately, many challenging reductive elimination processes limit the scope of coupling partners that can be used.

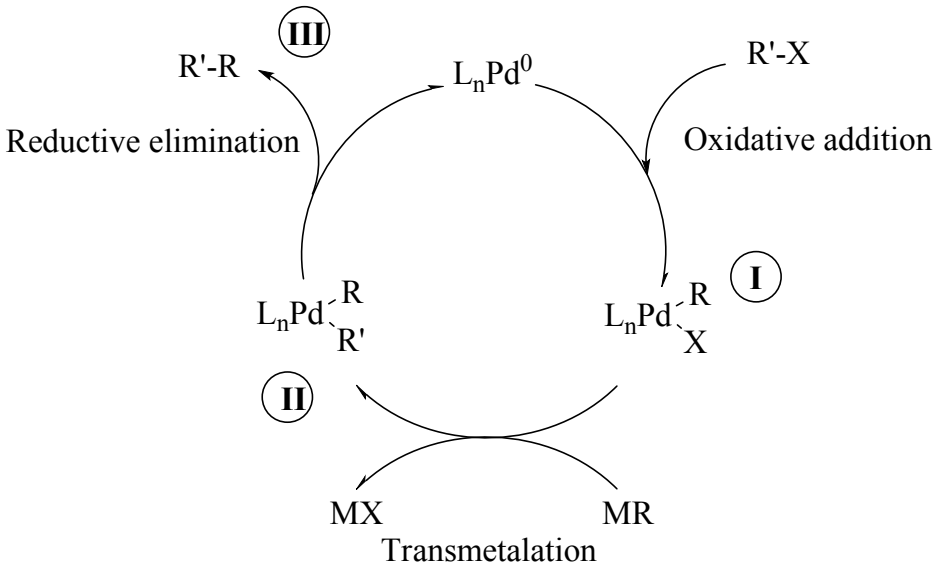


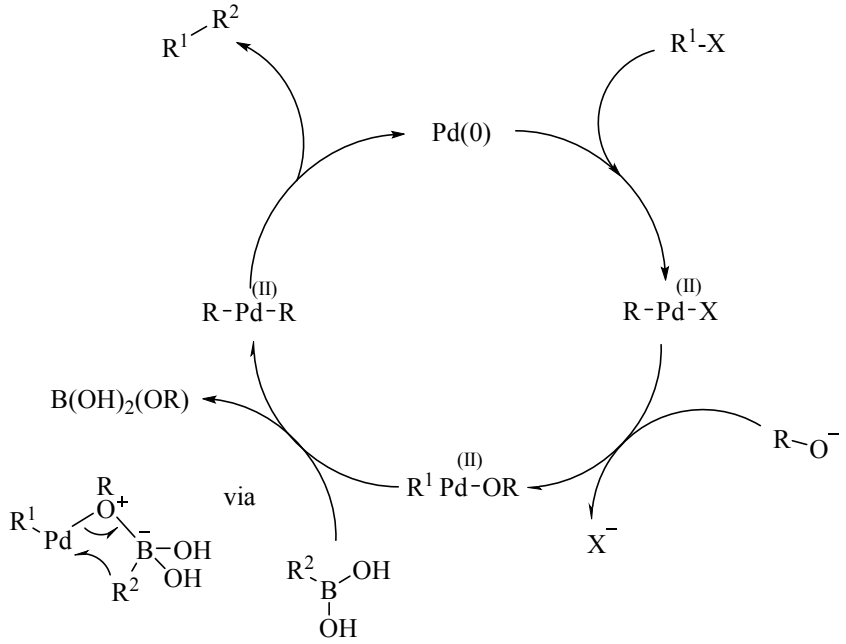
Figure 1. Simplified reaction mechanism of the cross-coupling reaction.

1.2 Suzuki-Miyaura coupling reaction

There are few classical cross-coupling reactions that have played a crucial role in the constructing novel chemical substances and became widely and fruitfully used by organic chemists: Suzuki-Miyaura reaction and Sonogashira coupling.

The first reaction uses organoboron compounds and organic halides under palladium catalysis and was developed by Suzuki and Miyaura at Hokkaido University in 1979 (**Scheme 1.2**).[8] Nowadays, not only aromatic halides act as a coupling partner in this coupling, but a various aryl pseudohalides can cross-couple readily with organoboron reagents, such as arylsulfonyl chlorides,[14] aryldiazonium tetrafluoroborates,[15] aryltrimethylammonium salts,[16] and phenolic derivatives (ethers,[17] carbamates[18][19] and carboxylates[20]).

Recently, a variety of organoboron reagents, e.g., trifluoroborates,[21] trialkoxyborates,[22] aryltrihydroxyborates,[23] has been developed. Low toxicity and stability toward water and air make them one of the best coupling agents to afford excellent yields of products.



Scheme 1.2 Possible reaction mechanism of Suzuki–Miyaura reaction.

However, with the development of an effective and powerful catalyst for the Suzuki–Miyaura cross-coupling reactions of less reactive aryl chlorides and organoboronic acids are no longer challenging. Nowadays, the current focus in the cross-coupling of aryl chlorides has switched to:

- reduce the amount of catalyst loadings,
- conduct reactions in environmentally benign conditions,
- further expanding the scope of substrates.

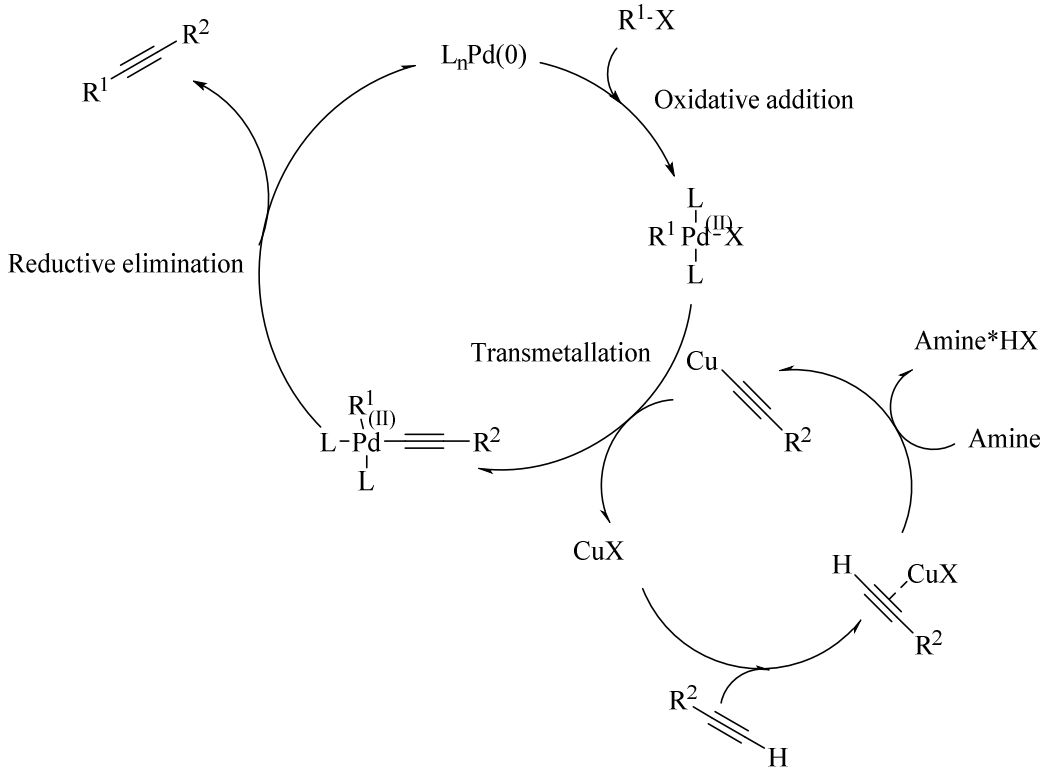
Although the Suzuki–Miyaura cross-coupling reaction is used predominantly for the syntheses of various indoles, quinolines, imidazoles, and pyridines, a number of particular challenges remain that significantly limit the scope of these reactions.

Basically, coordination of heteroatoms from the heterocycles to the metal catalyst may inhibit the catalytic cycle. Moreover, heteroaromatic boronic acids generally have poor reactivity and are not stable.

As a solution to these problems, chemists have tried to develop more effective ligands to accelerate these coupling reactions so as to minimize decomposition of boronic acids as a competitive process.

1.3 Sonogashira coupling reaction

First reported reaction on the cross-coupling reactions of acetylene or the terminal alkynes with aryl or alkenyl halides in the presence of palladium catalysts and monovalent copper salts was made by Sonogashira and Hagihara in 1975. Nowadays, this reaction is accepted as the most practical method for alkynylation of various organic halides. They demonstrated that the reactions improved the yields of the products under milder conditions by using the monovalent copper salts as co-catalysts (**Scheme1.3**).



Scheme 1.3 Possible reaction mechanism of Sonogashira reaction.

Most of the reported work on the Sonogashira cross-couplings relies on the use standard palladium catalysts, such as $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$. In the original paper, the amine base functioned not only as a reactant but also the solvent.

Aromatic iodides are the most commonly used organohalides under the Sonogashira conditions. On the contrary, unactivated aryl bromides typically require elevated temperatures.[24]

1.2 Tasks and motivation

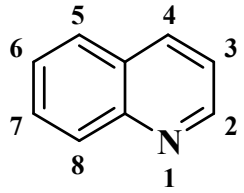
The group of Prof. Langer has made great efforts in chemistry of Suzuki-Miyaura reaction and therefore I focus on further investigation and development of palladium-catalyzed reactions of arylboronic acids with numerous heterocyclic substrates.

Due to the exceptional usefulness of cross-coupling reactions, my scientific goal was to develop and implement milder and more versatile reaction conditions in design and synthesis of new heterocycles, which are potentially interesting pharmacological active compounds.

2 Design and synthesis of novel 6*H*-chromeno[3,4-*c*]quinolin-6-ones

2.1 Introduction

2.1.1 Quinolines as major part of biologically important heterocyclic compounds



Quinoline was first described by German chemist Friedlieb Ferdinand Runge in 1834 by extracting it from coal tar.[25] Nowadays quinoline moiety is one of the most widely spread heterocyclic core fragment in naturally occurring compounds around us.

A great number of quinoline derivatives are very important in medicinal chemistry and pharmacy because of their bioactive properties.[26] In addition, certain quinoline-based compounds show anticancer,[27] antimalarial,[28] antifungal[29] and antibiotic activity.[30] Some examples of quinoline-based compounds, which have found their use as pharmaceutical agents, are shown in **Figure 2**.

In the heterocyclic chemistry arsenal of chemical transformations, there are certain successful synthetic methodologies were developed recently. Among them, we can surely admit transition metal-catalyzed cross-coupling reactions, which in recent decades have significantly expanded their application.

Chromenoquinolines combine both quinoline and coumarin moieties which are known to possess significant biological and pharmacological properties like bacteriostatic activity, anti-inflammatory effects and selective progesterone and glucocorticoid receptor modulators.[31,32]

Also, chromenoquinoline derivatives represent one such a unique class of hybrids found in the framework of several pharmacologically active compounds and natural products: santiagonamine,[33] schumanniophytine[34],[35] and goniothalines A,[36] contain this core structure (**Figure 3**).

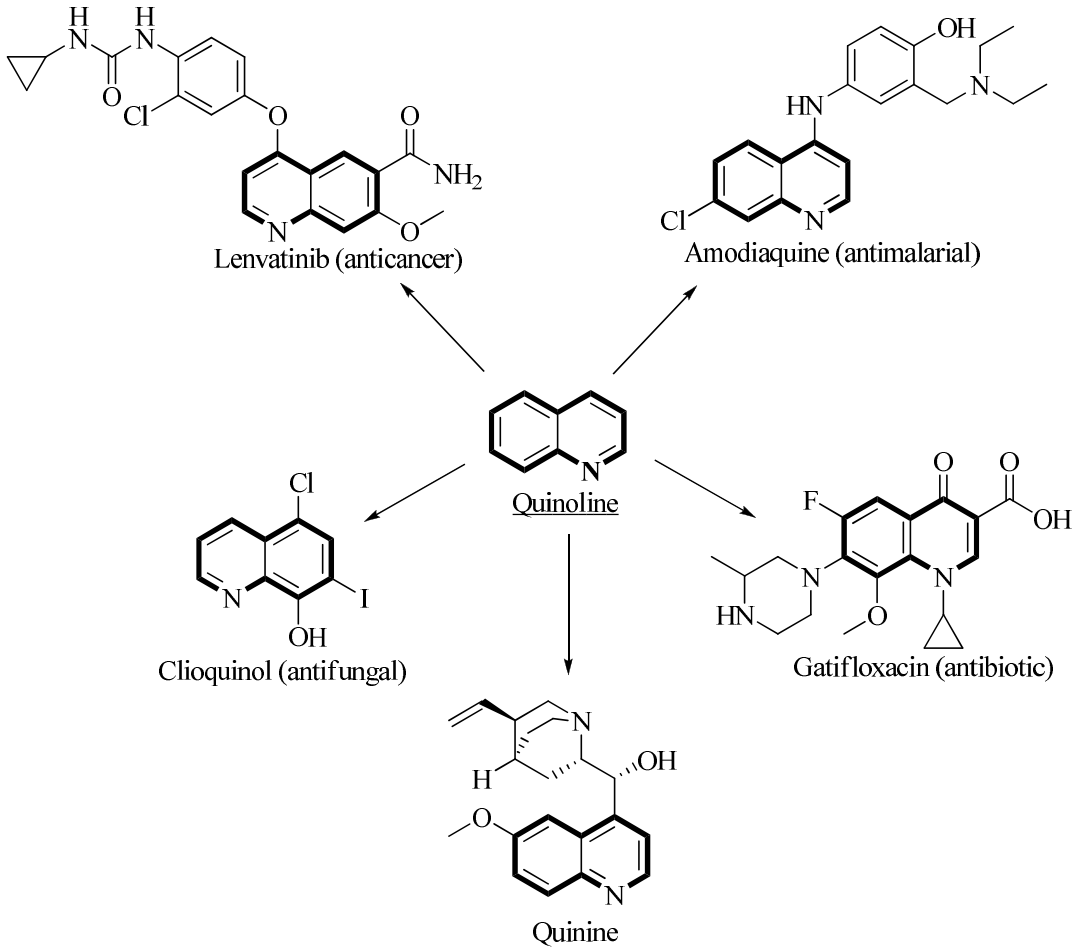


Figure 2. Biologically important quinoline derivatives.

Moreover, Zhang *et al*. showed structurally related 6*H*-chromeno[4,3-*b*]quinolin-6-ones exhibit potent cytotoxic activity and selectivity against colon cancer cells.[27] Asis *et al.* in the recent paper showed 4-arylated quinoline carboxylate compounds exhibited activity against *Plasmodium falciparum* and others resulted moderately active against *Trypanosoma cruzi*.[37] Hu *et al.* found quinoline-3-carboxamide containing sulfones as liver X receptor (LXR) agonists with binding selectivity for LXRβ and low blood-brain penetration.[38]

In addition, Cappelli and co-workers designed novel AT1 receptor antagonists bearing substituted 4-phenylquinoline moieties instead of the classical biphenyl fragment and synthesized as the first step of an investigation devoted to the development of new antihypertensive agents.[39] Claassen *et al*. found that 3-acetyl-6-bromo-4-(2-fluorophenyl)-2(1*H*)-quinolinones rapidly activate the apoptotic cascade and can efficiently target cancer cells.[40] Also, in the research of Illig *et al*.[41] series

of 3,4,6-substituted 2-quinolones evaluated as potent kinase inhibitors in the treatment of certain types of cancer.

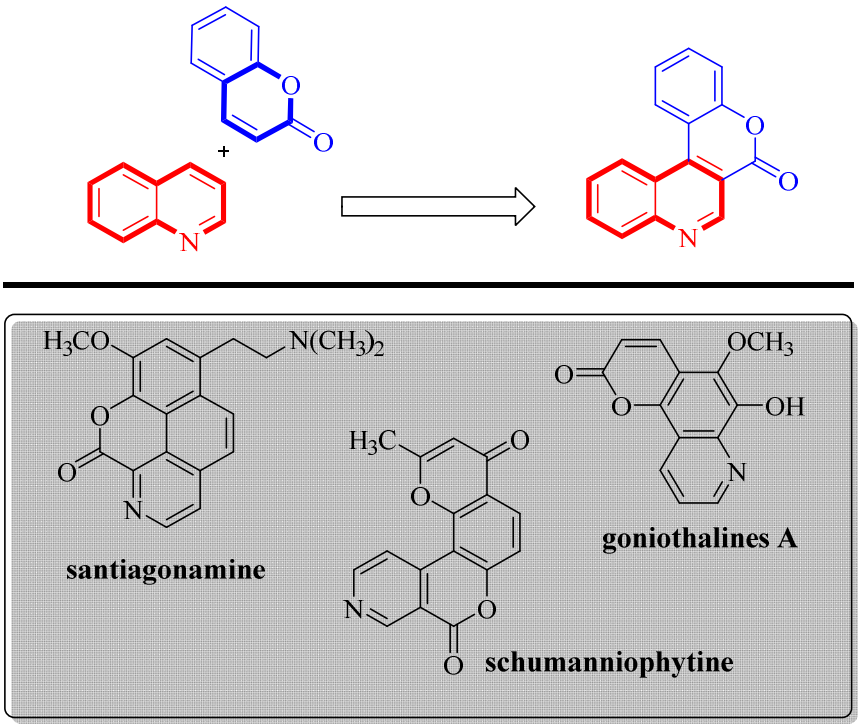
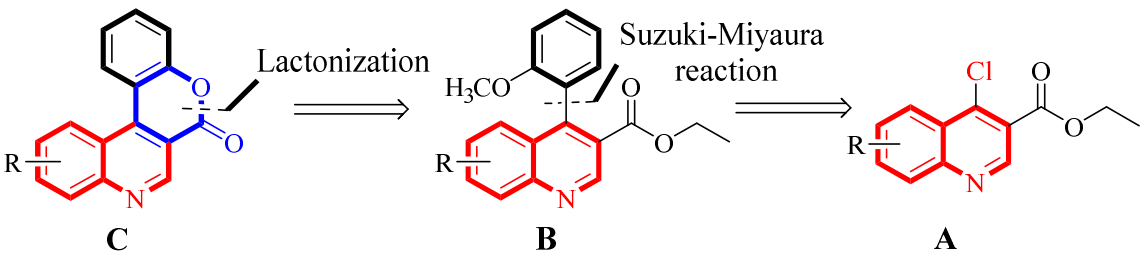


Figure 3. Biologically important heterocyclic lactones.

Thus, the structural features and the pharmaceutical applications of chromenoquinolines motivate intense research for the development of novel methodologies of their synthesis, including palladium catalysis. Currently one of the major issues is to find most suitable, convenient and straightforward methods of synthesis of novel quinoline compounds.

2.2 Synthesis of starting materials

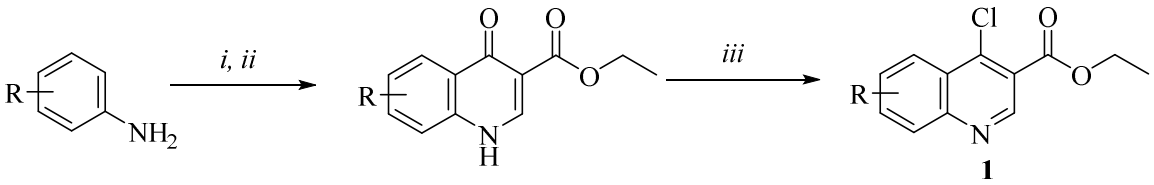
Based on retrosynthetic analysis of desired ring systems, we envisaged the synthetic strategy depicted in Scheme 2.2:



Scheme 2.2: Retrosynthetic approach to the 6*H*-chromeno[3,4-*c*]quinolin-6-ones.

The synthesis includes, at first, preparation of ethyl 4-chloroquinoline-3-carboxylates (**A**), the second step suggests Suzuki-Miyaura reaction with ortho-methoxyarylboronic acid (**B**) and, finally, lactonization leading to target molecules (**C**). Several methods have been reported in the literature for the synthesis of 4-substituted quinolines, which are modifications of well-known classic quinoline-forming reactions (Skraup, Rhiem, Conrad-Limpach, Friedländer, Knorr, and Combes).[42] Among them, the most efficient method was that the 4-position substituent on the quinoline ring was introduced first after the formation of quinoline ring via metal-catalyzed reactions.[43][44] The key step of my approach involves substitution at 4-position of the quinoline core using Suzuki-Miyaura reaction. To the best of my knowledge, the related strategy has previously successfully applied to the synthesis of thienochromenones in the group of Prof. P. Langer.[45]

With this concept in hand, I have started the investigation of the synthesis of starting compounds.



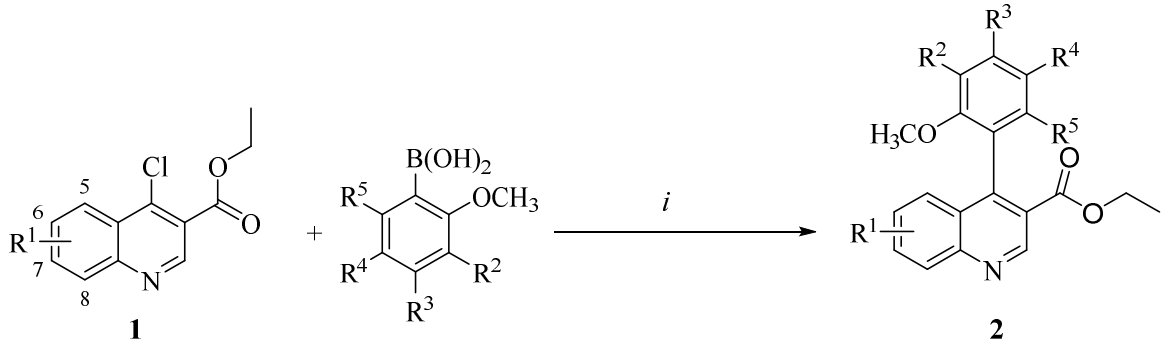
Scheme 2.2.1: Synthesis of ethyl 4-chloroquinoline-3-carboxylates **1**.
Reaction conditions: (*i*) (2-ethoxymethylene)malonate, EtOH, reflux, 5 h; (*ii*) Ph_2O, reflux 0.5-1 h;.(*iii*) $POCl_3$, neat, 110 °C, 1-2 h.

According to the literature data, ethyl 4-chloroquinoline-3-carboxylates were synthesized using a previously reported general route (**Scheme 2.2.1**). Briefly, substituted anilines were subjected to the reaction with (2-ethoxymethylene)malonate to yield the corresponding diethyl 2-((arylamino)methylene)malonates. In the next step prepared compounds were benzannulated via Gould−Jacobs cyclization in the diphenyl ether at 240 °C within 1 hour (prolonged heating caused lower yield).[46],[47] The final step includes chlorination with neat $POCl_3$. In order to expand the products' scope, six different 4-chloroquinoline derivatives **1** were synthesized.

2.3 Synthesis of 4-arylated quinolines via Suzuki-Miyaura reaction

Having access to the synthesized ethyl 4-chloroquinoline-3-carboxylates I studied the synthesis of desired 4-arylquinolines **2** via Suzuki-Miyaura cross-coupling reaction (**Scheme 2.3**).

As a source of Pd, I used $Pd(PPh_3)_4$, as the most common catalyst for such type of transformations. My initial trials included utilization of toluene or 1,4-dioxane as a solvent and potassium carbonate or potassium phosphate as a base, which is obligatory to use for hydrochloric acid neutralization and to activate the boronic acid. The mixture of 4-chloroquinoline-3-carboxylate (**1**), 1.2 equiv. of *ortho*-methoxyarylboronic acid, 5 mol% of $Pd(PPh_3)_4$ and 2.5 equiv. of K_2CO_3 was heated in DMF up to 130 °C under argon atmosphere. After 10-12 hours, no further product formation was observed (according to TLC) and compounds **2** were isolated in the amount of 43-94 % overall yield (**Table 2.3**).



Scheme 2.3: Synthesis of compounds **2**.

Reaction conditions: (*i*) 2-methoxyarylboronic acid (1.2 equiv.), $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (2.5 equiv.), DMF, 130 °C, 10 - 12 h.

Table 2.3 Synthesis of compounds **2**.

2	**R^1**	**R^2**	**R^3**	**R^4**	**R^5**	**Yield, (%)[a)]**
2a	6-H	OCH_3	-	-	-	94
2b	6-H	-	-	OCH_3	-	89
2c	6-H	-	-	-	OCH_3	43
2d	6-H	OCH_3	OCH_3	-	-	84
2e	6-CH_3	-	-	-	-	82

2f	6-CH_3	OCH_3	-	-	-	94
2g	6-CH_3	-	-	OCH_3	-	95
2h	6-CH_3	OCH_3	OCH_3	-	-	55
2i	6-CH_3	-	-	F	-	88
2j	6,8-CH_3	-	-	-	-	60
2k	6,8-CH_3	-	-	OCH_3	-	80
2l	6,8-CH_3	OCH_3	-	-		63
2m	6,8-CH_3	OCH_3	OCH_3	-	-	75
2n	6,8-CH_3	-	-	F	-	70
2o	6-F	-	-	-	-	89
2p	6-F	OCH_3	-	-	-	87
2q	6-F	-	-	OCH_3	-	86
2r	6-F	OCH_3	OCH_3	-	-	87
2s	6-F		-	-	OCH_3	54
2t	6-F	-	-	F	-	87
2u	6-NO_2	-	-	OCH_3	-	51
2v	7-Cl	-	-	-	-	61
2w	7-Cl	OCH_3	OCH_3	-	-	72
2x	7-Cl→7-(2,5-$OCH_3C_6H_3$-)	-	-	OCH_3	-	65[b)]

a) Yield of isolated products.

b) Compound **2x** is a product of substitution of both chlorine atoms.

Among other methods, including ^1H, ^{13}C NMR, IR, mass spectrometry, the structure of **2h** was independently confirmed by X-ray crystallographic analysis (**Figure 4**). Furthermore, the aryl substituent of the molecule twisted out to planar quinoline core with torsion angle of 76-78°.

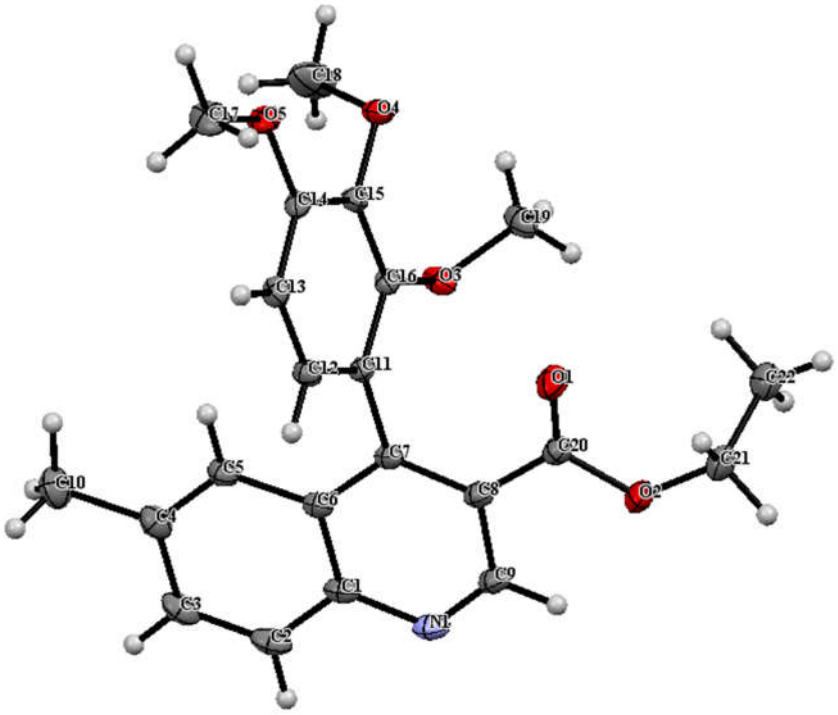


Figure 4. ORTEP of ethyl 6-methyl-4-(2,3,4-trimethoxyphenyl)quinoline-3-carboxylate **2h** (50% probability level).

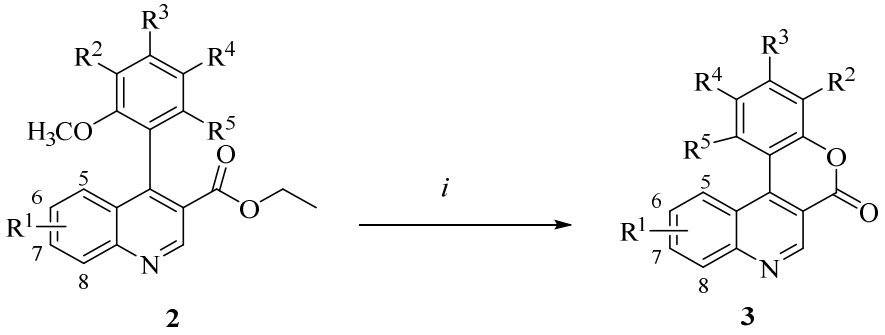
In the ^{13}C NMR spectra, signals of carbonyl group appeared at δ = 165-167 ppm. Expectedly, in the case of 2,6-dimethoxy substituents, product yield was lower due to the sterical reasons.

2.4 Synthesis of 6*H*-chromeno[3,4-*c*]quinolin-6-ones

The synthesis of condensed thienocoumarins by Suzuki-Miyaura reaction/lactonization tandem protocol was previously developed in a group of Prof. Dr. P. Langer. During my research, I studied next the transformation of ethyl 4-arylquinoline-3-carboxylates **2** into lactones **3** by this method.

The most commonly used reagent for sequential demethylation and lactonization boron tribromide was chosen for this approach. According to the literature data, among any other Lewis acid reagents – BBr_3 – is more suitable for this reaction due to the ability to cleave ethoxy group in the quinoline core moiety.[48],[32] With slightly

modified conditions, the reaction proceeded smoothly at 0 °C within 6 hours and the compounds **3a-x** were obtained in good to excellent yields.



2 **3**

Scheme 2.4: Synthesis of compounds **3**.

Reaction conditions: (*i*) BBr_3, CH_2Cl_2, 0 °C – 25 °C.

6*H*-chromeno[3,4-*c*]quinolin-6-ones are mostly light yellow-colored compounds, moderately soluble in the mixture chloroform-methanol and partially in dimethylformamide (DMF) and dimethylsulfoxide (DMSO). By reason of low solubility in DMSO-d_6, investigation of ^{1}H and ^{13}C NMR measurements were performed at higher temperatures (100 °C, compounds **3a-e**).

Table 2.4. Synthesis of compounds **3**.

3	**R^1**	**R^2**	**R^3**	**R^4**	**R^5**	**Yield, (%)$^{a)}$**
3a	6-H	OH	-	-	-	88
3b	6-H	-	-	OH	-	86
3c	6-H	-	-	-	OH	43
3d	6-H	OH	OH	-	-	90
3e	6-CH_3	-	-	-	-	76
3f	6-CH_3	3-OH	-	-	-	81
3g	6-CH_3	-	-	OH	-	87
3h	6-CH_3	OH	OH	-	-	90

3i	6-CH_3	-	-	F	-	55
3j	6,8-CH_3	-		-	-	79
3k	6,8-CH_3	OH	-	-	-	82
3l	6,8-CH_3	-	-	OH	-	86
3m	6,8-CH_3	OH	OH	-	-	65
3n	6,8-CH_3	-	-	F	-	89
3o	6-F	-	-	-	-	87
3p	6-F	OH	-	-	-	65
3q	6-F	-	-	OH	-	78
3r	6-F	-	-	-	OH	25
3s	6-F	OH	OH	-	-	70
3t	6-F	-	-	F	-	85
3u	6-NO_2	-	-	OH	-	81
3v	7-Cl	-	-	-	-	83
3w	7-Cl	OH	OH	-	-	78
3x	7-(2,5-OHC_6H_3)	-	-	OH	-	72

[a] Yield of isolated product.

In most cases, the end product could be isolated by simple filtration of the formed precipitate. All desired 6*H*-chromeno[3,4-*c*]quinolin-6-ones were obtained in moderate to good yields.

2.5 Conclusions

In conclusion, I described a facile and efficient method for the preparation of 6*H*-chromeno[3,4-*c*]quinoline-6-ones by a two-step synthetic strategy starting from various ethyl 4-chloroquinoline-3-carboxylates via Suzuki-Miyaura reaction followed

by lactonization reaction. Desired compounds were obtained under mild reaction conditions and with good yields.

The products obtained during this study might be of pharmacological relevance.

3. Site-selective synthesis of ethyl 4,7-dichloroquinoline carboxylates

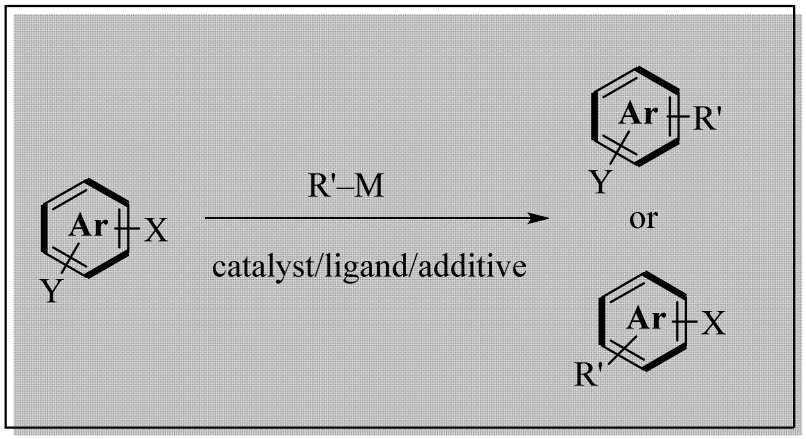
3.1 Introduction

As it was shown in the previous chapter, functionalized quinolines have various pharmacological and medical applications and are important in many biological processes.

Continuing my initial study of 4-chloroquinolines, I turned my attention to polyhalogenated quinoline substrates. In order to study the possibility of successive halogen substitution in Suzuki-Miyaura reactions, I chose ethyl 4,7-dichloroquinoline-carboxylate as a model substrate. However, the choice of conditions for a selective functionalization remains challenging task for research chemists (**Scheme 3.1**).

This substrate attracts additional interest because some functionally-substituted quinolines are known to possess a biological activity.[49–52] Recently, series of 4-arylated quinoline-3-carboxylic acids developed by Kühne *et al.* showed activity against atherosclerosis.[53] Barate *et al*. recently reported on the antioxidant activity of 4-arylquinolines in Alzheimer's treatment.[54] Chakraborti *et al*. have synthesized a set of new quinolines with antitubercular activity against *Mycobacterium tuberculosis*.[51]

Furthermore, site-selective functionalization of 4,7-dichloroquinolines is interesting in my research due to the results by Milbank *et al.* as such compounds were found as orally active compounds with high affinity for the MPEP (allosteric modulator of the metabotropic glutamate receptor subtype 5) binding site.[55] In 2011, Wolkenberg and co-workers reported novel 3,6-diarylquinolines as therapeutics for the treatment of proliferative diabetic retinopathy and exudative age-related macular degeneration.[56] LaVoie *et al.* reported 6- and 7-substituted 3-hydroxyquinolin-2(1*H*)-ones as a useful scaffold for the development of endonuclease inhibitors that could block the cap-snatching associated with *influenza A* replication.[57]



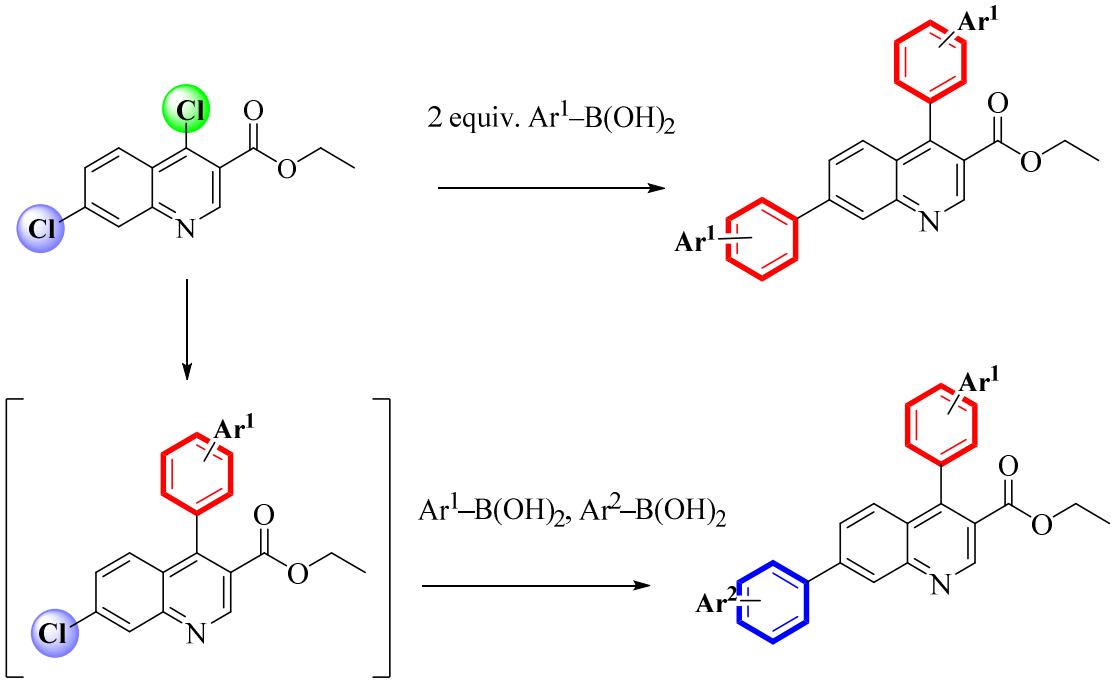
Scheme 3.1 Chemoselective and site-selective cross-coupling of organic dihalides.

Using a wide experience in constructing of a variety of heterocyclic systems (indoles, chromones, pyrroles, thiophenes and quinolones) via palladium-catalyzed reactions in the group of Prof. P. Langer,[58–61] I decided to explore reactivity of ethyl 4,7-dichloroquinoline carboxylate (**Scheme 3.1.1**), which is available from the previous project (see **Chapter 2**). Functionalization of 4,7-dichloroquinolines by Suzuki reaction opens a simple route to polysubstituted quinolines with various functional groups in the aryl rings. Moreover, routes to 4,7-diarylquinolines have been less studied in the past.

Site-selective cross-coupling of organic dihalides has been based on the "substrate-controlled" strategy, in which the selectivity between the two halogen atoms is controlled by the structures of the substrates. There are three general pathways:

- the reaction preferentially occurs at the less sterically hindered position;
- the reaction preferentially occurs at the more deficient carbon atom;
- the catalyst is directed by a coordination of a functional group to a specific position.

Computational and mechanistic studies on the factors influencing site-selectivity in polyhaloheteroaromatics have been reported, which conduct these factors with the strength of the carbon-halogen bonds and energy of molecular orbitals.[62]-[64]

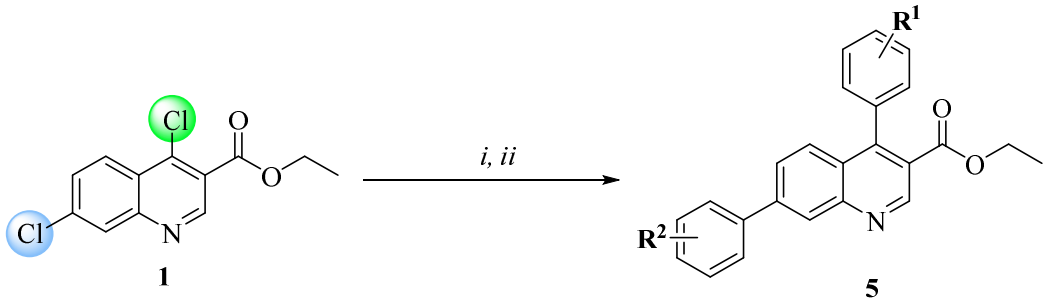


Scheme 3.1.1. Suzuki functionalization of 4,7-dichloroquinolines.

3.2 Site-selective one-pot synthesis of 4,7-diarylated quinolines

Having achieved an effective method to prepare 4-substituted *o*-methoxyphenyl derivatives, I turned my attention towards the site-selective Pd-catalyzed cross-coupling reactions for the synthesis of 4,7-diarylsubstituted quinolines.

My investigations into Suzuki couplings (**Scheme 3.2**) revealed that chlorinated quinolines exhibited reactivity patterns typical of heteroaromatic halides. The use of $Pd(OAc)_2$ as a palladium source for the coupling with arylboronic acids provided the desired 4,7-bisarylated quinolines in good yield (**Table 3.2**). The use of ligands known to activate aromatic chlorides towards oxidative addition afforded improved reactivity. The catalyst combination of $Pd(OAc)_2$ and XPhos, with K_3PO_4 as the base, enabled the successful regioselective Suzuki-Miyaura reaction between chlorinated quinolines and both electron-rich and electron-deficient boronic acids (**Table 3.2**).



Scheme 3.2. One-pot synthesis of compounds **5**.

Reaction conditions: (*i*) arylboronic acid (1.1 equiv.), $Pd(PPh_3)_4$ (2 mol%), K_2CO_3 (2.5 equiv.), DMF, 130 °C, 10 - 12 h; (*ii*) arylboronic acid (1.2 equiv.), $Pd(OAc)_2$ (2mol%), Xphos (4 mol%), K_2CO_3 (2.5 equiv.), DMF, 130 °C, 10-12 h.

Table 3.2 Synthesis of compounds **5**.

5	**R^1**	**R^2**	**Yield, %[a)]**
5a	3,5-$OCH_3C_6H_3$-	4-$EtOC_6H_4$-	60
5b	C_6H_5-	4-*t*-BuC_6H_4-	62
5c	4-EtC_6H_4-	4-$CH_3C_6H_4$-	70
5d	3-$OCH_3C_6H_4$-	4-$CF_3C_6H_4$-	77
5e	4-$CF_3C_6H_4$-	4-$CF_3OC_6H_4$-	80
5f	3-$OCH_3C_6H_4$-	4-$CH_3C_6H_4$-	88
5g	3,5-$CH_3C_6H_3$-	4-$OCH_3C_6H_4$-	58
5h	C_6H_5-	thiophen-3-yl	50
5i	C_6H_5-	2,3-$OCH_3C_6H_3$-	82
5j	4-$CF_3C_6H_4$-	3-$OCH_3C_6H_4$-	85
5k	4-$CH_3C_6H_4$-	3-thienyl-	84
5l	4-*i*-PrC_6H_4-	4-$OCH_3C_6H_4$-	85
5m	2,3-$OCH_3C_6H_3$-	4-FC_6H_4-	51

5n	3-FC_6H_4-	4-FC_6H_4-	57

[a] Yield of isolated products.

In the case of **5c**, the structure was independently confirmed by X-ray single crystal analysis. Aryl rings in positions 4 and 7 are twisted to planar quinoline core. The torsion angle between 4-ethylphenyl substituent and quinoline moiety lies within 82.94° – 84.70°. The values of angles of 7-*p*-tolyl fragment lie within 33.63° – 34.38°.

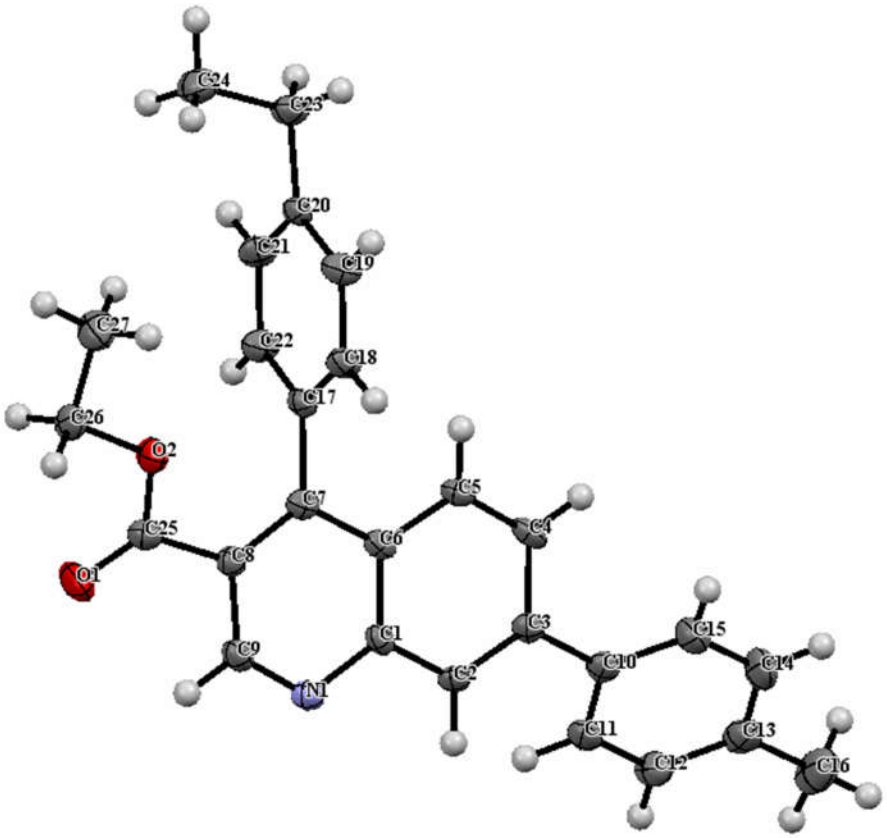
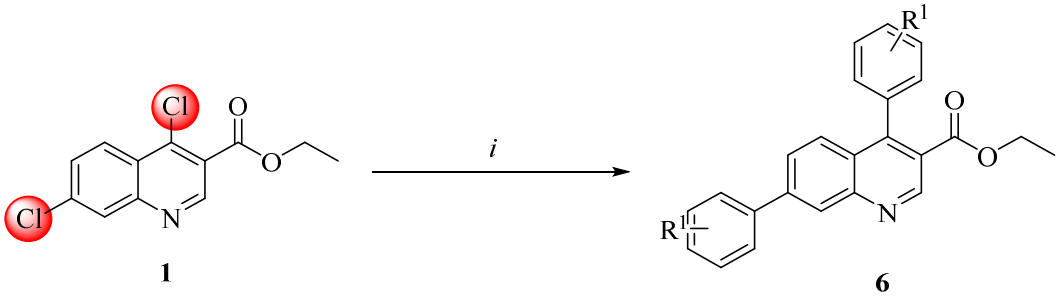


Figure 5. ORTEP of ethyl 4-(4-ethylphenyl)-7-*p*-tolylquinoline-3-carboxylate **5c** (50 % probability level).

3.3 Synthesis of bisarylated products

Having obtained results in the successful regioselective substitution of chlorine atoms, I focused my attention to the double-substituted quinolines. Having in hand effective catalyst and palladium source from initial studies, I implemented conditions for substitution chlorine atom at the position 7. Thus, the reaction of starting quinoline

1 with 2.2 equivalents of boronic acid, $Pd(OAc)_2$ (2 mol%), Xphos (4 mol%), K_2CO_3 (2.5 equiv.) in DMF gave desired product in good to excellent yields (**Scheme 3.3**, **Table 3.3**).



Scheme 3.3. Synthesis of compounds **6**.

Reaction conditions: (*i*) arylboronic acid (2.2 equiv.), $Pd(OAc)_2$ (2 mol%), Xphos (4 mol%), K_2CO_3 (2.5 equiv.), DMF, 130 °C, 10 - 12 h;

Table 3.3. Synthesis of compounds **6**.

6	**R^1**	**Yield, %**[a)]
6a	3,5-$CH_3C_6H_3$-	95
6b	thiophen-3-yl	87
6c	3-FC_6H_4-	86
6d	C_6H_5-	88
6e	4-$CF_3C_6H_4$-	56
6f	4-EtC_6H_4-	83
6g	4-$CH_3C_6H_4$-	87
6h	4-$OCH_3C_6H_4$-	86
6i	4-*t*-BuC_6H_4-	79
6j	4-$CF_3OC_6H_4$-	68

[a)] Yield of isolated products

The position of halogen substitution, in this case, is driven by electronic effects in quinoline ring system. The halogen atom at the position 7 is less reactive towards nucleophilic substitution than at the position 4, which is more reactive in these reactions also due to its *ortho* location to the ester group with its π-acceptor effect. In the oxidative addition step Pd(0) acts as a nucleophile and will preferentially attack the most electron-deficient position (**Figure 6**). Since insertion step is considered to be the selectivity-determining one,[65,66] the site-selectivity of the reaction is realized through this mechanism.

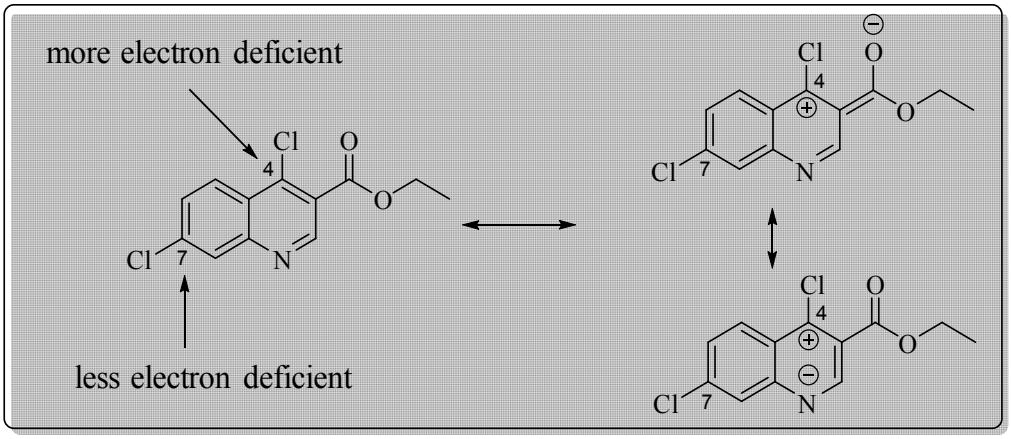


Figure 6. Possible explanation for the site-selective reactions.

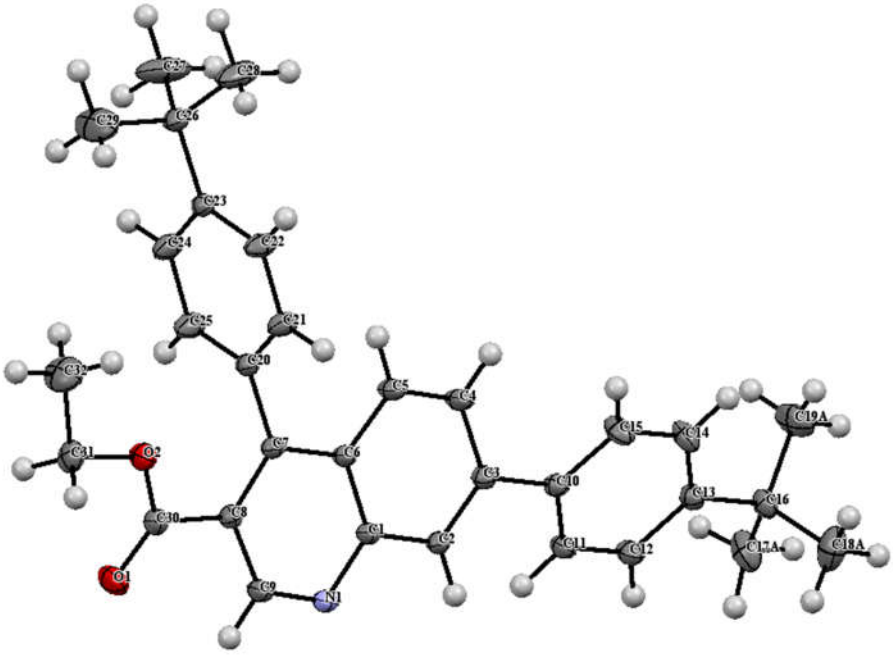


Figure 7. ORTEP of ethyl 4,7-bis(4-tert-butylphenyl)quinoline-3-carboxylate **6i** (50% probability level).

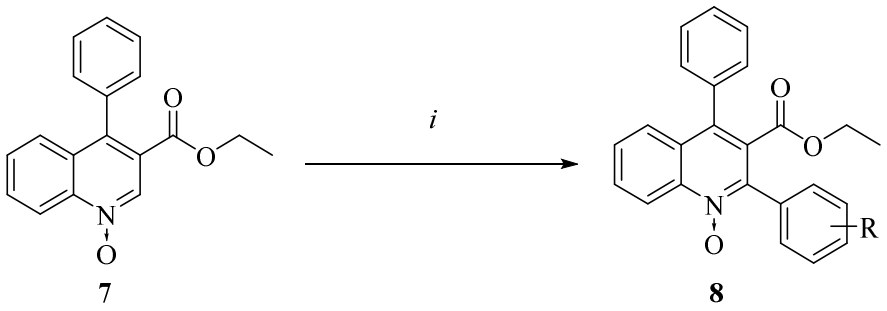
Furthermore, the structure of **6i** was identified also by X-ray single crystal analysis (**Figure 7**). In the current framework, I observed a planar core of quinoline core unit. As seen from crystallographic data, the torsion angle between quinoline core and 4-*t*-butylphenyl substituent at position 4 is 79.50°–80.24° and position 7 – 28.91°–28.93°, respectively.

It is important to mention, ethoxycarbonyl fragment at position 3 of quinoline core can be transformed to many other functionalities, which potentially gives wider spectra of compounds.[38]

Additional attempts to explore the further scope of 4- or 4,7-halogenated quinolines were done through N-oxide derivatives of 4-phenylquinoline. It gives another route for the biologically active class of compounds, namely, heterocyclic N-oxides.[67]

Numerous examples of heterocyclic N-oxides have shown antimicrobial, antibacterial, antitumor, and other activities.[68] The C−H functionalization by transition metal catalysis provides an efficient method for the straightforward synthesis of complex molecules with a quinoline scaffold.[69–73] Moreover, by simple deoxygenation under mild conditions, the N-oxide moiety could be used to introduce a wide range of other functional groups.

Following the similar procedure,[74] the initial N-oxide (**7**) was prepared by the reaction of ethyl 4-phenylquinoline-3-carboxylate with MCPBA in CH_2Cl_2 at 0 °C.

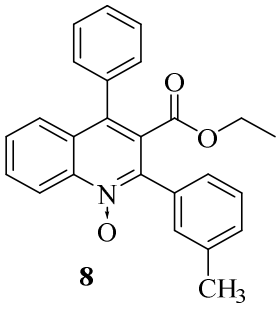


7 **8**

Scheme 3.3.1. Synthesis of compounds **8**.

Reaction conditions: (*i*) bromoarene (0.5 equiv.), $Pd(OAc)_2$ (5 mol%), P*t*Bu_2Me·HBF_4 (5 mol%), K_2CO_3 (2 equiv.), toluene, 110 °C, 10 h.

With this positive result in hand, I set the reaction of corresponding N-oxide with 3-bromotoluene, $Pd(OAc)_2$ (5 mol%), P*t*Bu_2Me·HBF_4 (5 mol%), K_2CO_3 in toluene at 110 °C for 10 h to give desired product **8** in 97% yield (**Scheme 3.3.1**).



8

The C2-substitution pattern was confirmed by means of NMR spectroscopy. The absence of the typical signal of 2-H proton in reaction product at 9 ppm and increased number of aromatic protons clearly indicate the substitution with aryl fragment and successful C-H activation. Additionally, the singlet of methyl group from the *m*-tolyl functionality appears at 2.4 ppm ($CDCl_3$) (**Figures 8**, **9**).

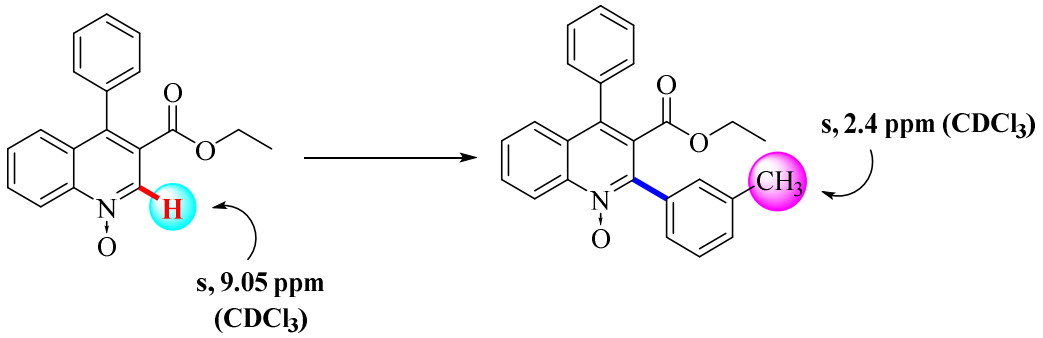


Figure 8. Observations from NMR experiments.

Functionalization of position 2 of N-oxide proceeded via *ortho*-selective C-H activation that exhibited high regioselectivity.

In research of Fagnou group catalytic process of N-oxide functionalization proposed to proceed through a 6-membered inner-sphere concerted metallation-deprotonation (CMD) transition state, generating the palladium biaryl species that goes on to the reductive elimination step to give product and regenerate the Pd(0) catalyst. Notably, this pathway also did not involve precoordination of oxygen atom of the N-oxide to palladium.[75]

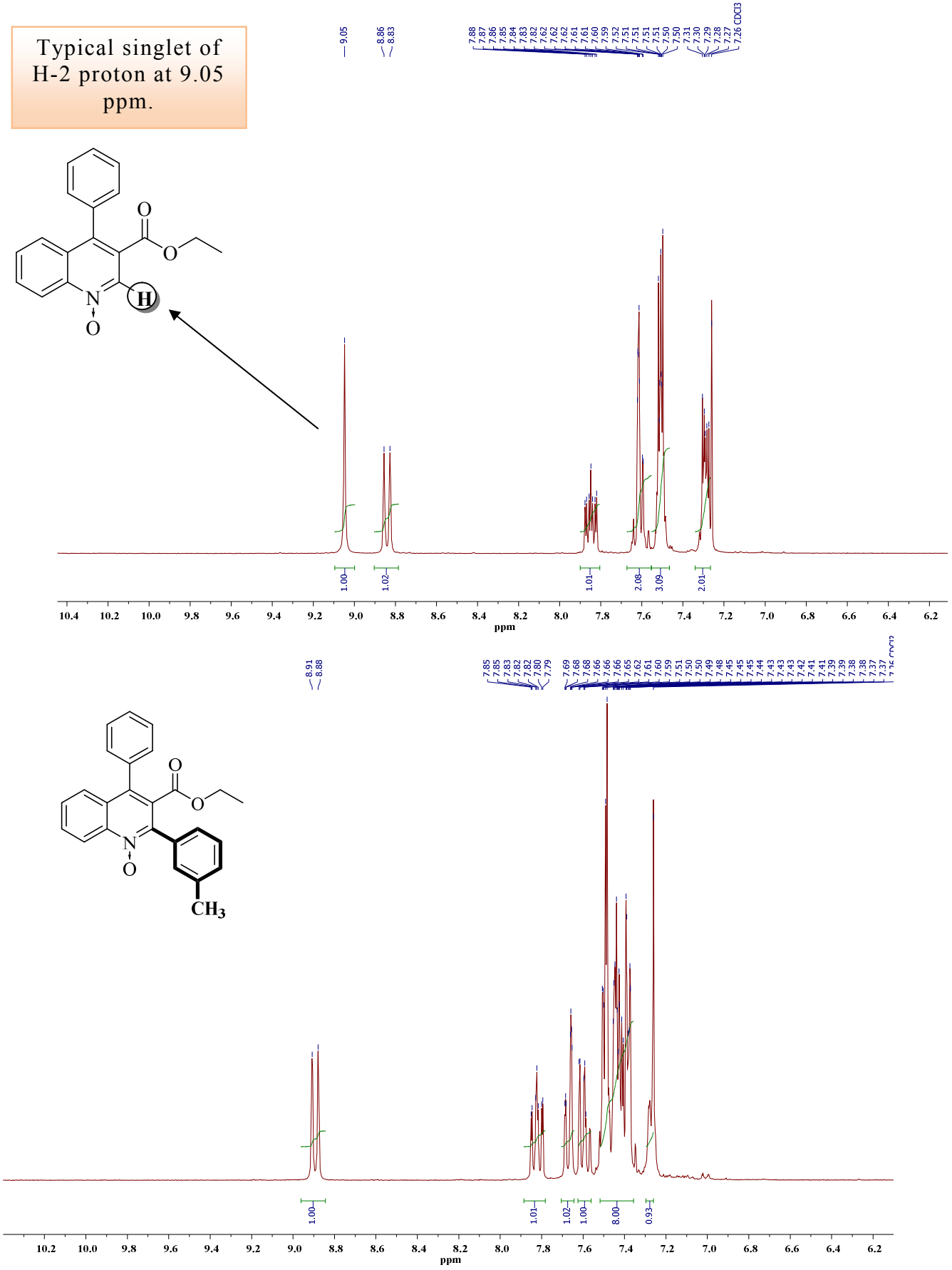


Figure 9. Comparison of ^{1}H NMR spectra for **8** and **9** (aromatic region only).

3.4 Conclusions

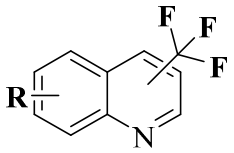
In conclusion, I have described a facile and efficient method for the site-selective preparation of quinolines by a one-pot synthetic strategy starting from 4,7-dichloroquinolines via Suzuki-Miyaura reaction. Desired products obtained with excellent regioselectivity, under mild reaction conditions, and with good yields.

The scope and limitation of the method were studied and the structures of two products were unambiguously confirmed by a single-crystal X-ray diffraction. In addition, one example of 4-substituted N-oxide quinoline derivative was functionalized via palladium mediated C−H arylation.

4. Design and synthesis of 2-aryl-4-(trifluoromethyl)-quinolines and different substituted 2-(ethynyl)-4-(trifluoromethyl)-quinolines

4.1 Introduction

Recent years a reasonable interest has been focused towards the synthesis of various fluorinated quinoline compounds.



Fluorine-containing molecules are of particular interest in the fields of biomedicine, agriculture, and material sciences.[76–78] Incorporation of a fluorine atom into heterocycles is known to enhance the biological activity and provide some other unique properties, like modulation of pK_a, changing of hydrophobic interactions, solubility, hydrogen bonding, and lipophilicity. All these properties or their combinations can improve potency or selectivity of drug molecules.[79] The quinoline scaffold has been used for a long time as a basic structure for the search of synthetic antimalarial drugs, such as mefloquine. The antineoplastic drug Brequinar® and its analogs proved to be useful in transplantation medicine,[79] for the treatment of rheumatic arthritis[80] and psoriasis.[81]

A new series of 8-trifluoromethyl quinolines were evaluated for antitubercular and antibacterial activity in a recent paper by Dalimba *et al*.[82] A series of 4-trifluoromethylquinolinones synthesized by Higuchi *et al*. were evaluated in an androgen receptor transcriptional activation assay and can be used in endocrine therapies to treat muscle wasting and osteoporosis.[83,84] Bowers and colleagues reported series of fluoro- and trifluoromethylquinoline-based compounds as effective neuroprotective agents.[85] Gasparini *et al*. in his early work in 1998 have shown anti-hyperalgesic activity of MPEP (synthetic mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine).[86,87] mGluR5 is a protein-coupled receptor, which plays important role in several disorders of the central nervous system such as

schizophrenia, depression, anxiety, Alzheimer, and Parkinson's disease.[88–91] Recently, different kinds of mGluR5 – NAMs – such as ADX10059 and AFQ056 have been discovered and known to be effective for Fragile X syndrome, chronic digestive disease (GERD), and migraine.[92] Many of mGluR5 antagonists contain an alkyne subunit as a key structural component. Therefore, much effort has been focused on the synthesis of compounds bearing acetylene itself or its isostere (**Figure 10**).

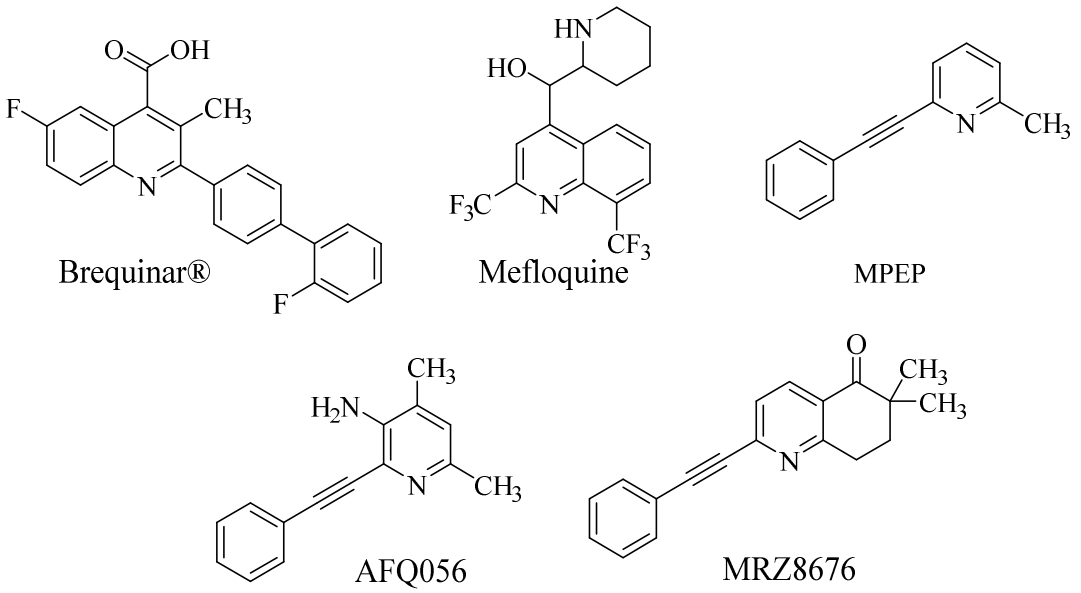
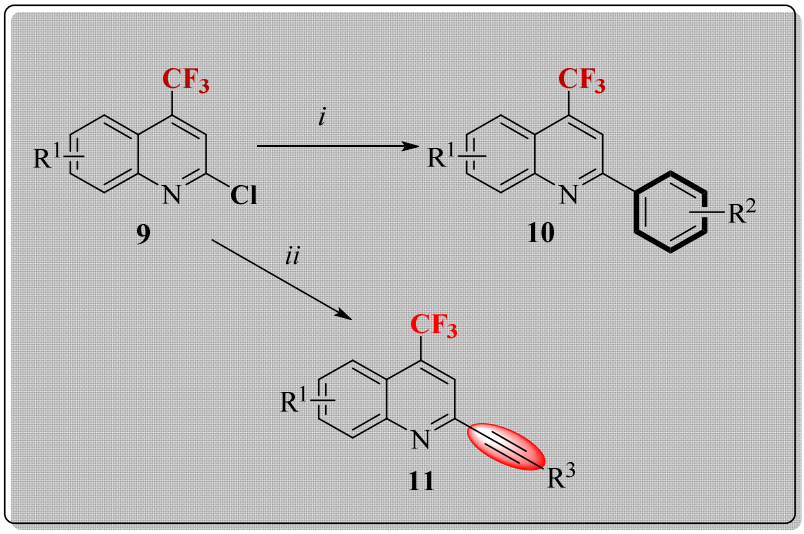


Figure 10. Examples of various quinoline-based drugs.

Previously in a group of Prof. P.Langer was developed the synthesis of 4-chloro-3-(trifluoroacetyl)coumarins, a novel fluorine-containing 1,3-dielectrophiles on the basis of commercially available 4-hydroxycoumarin by the reaction with a number of *o*-, *m*- and *p*-substituted anilines.[93]

4.2 Synthesis of starting materials

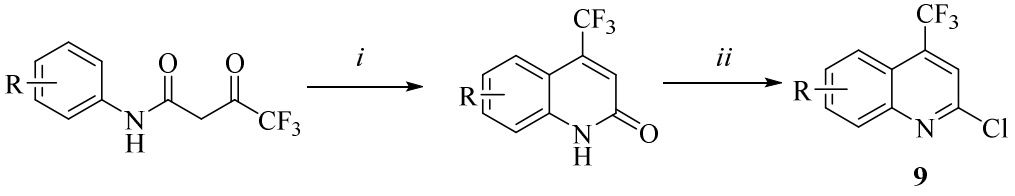
According to detailed analysis of literature concerning the chemistry of quinolines bearing trifluoromethyl group (CF_3-), I focused my attention on the synthesis and modification of 4-CF_3-substituted chloroquinolines via palladium-catalyzed reactions.



Scheme 4.2. Synthetic routes to 2-substituted fluoroquionolines via (*i*) Suzuki-Miyaura and (*ii*) Sonogashira protocols.

For this purpose, I used the already known 4-trifluoroquinoline-containing building block **9**. The synthesis of 2-chloro-4-(trifluoromethyl)quinolines by subsequent reaction of ethyl trifluoroacetoacetate with anilines, using a related strategy, was previously reported.[94]

Condensation of anilines with ethyl trifluoroacetoacetate have been established to give the corresponding 4,4,4-trifluoro-3-oxobutane substituted anilides, known precursors in the synthesis of 4-(trifluoromethyl)quinolinones. Namely, 4-fluoromethylquinolin-2-ones were obtained regioselectively in moderate to good yields by acid assisted intramolecular ring closure reaction of the corresponding N-aryl-3-oxo-polyfluoroalkanamides. Heating of these compounds with phosphoryl trichloride easily affords desired 2-chloro-4-(trifluoromethyl)quinolines **9**. In this manner 4 differently substituted 2-chloro-4-(trifluoromethyl)quinolines were synthesized (**Scheme 4.2.1**).

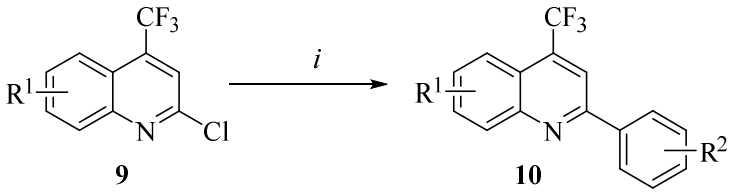


Scheme 4.2.1. Preparative route to compounds **9**.

Reaction conditions: (*i*) conc. sulfuric acid, 90 °C, 1h.; (*ii*) $POCl_3$, reflux, 1.5 h.

4.3 Suzuki-Miyaura reaction of 2-chloro-4-(trifluoromethyl)quinolines

The next step of my research was conducting cross-coupling reactions of obtained 2-chloro-4-(trifluoromethyl)quinolines with arylboronic acids. It was found that the Suzuki-Miyaura reaction of **9** with arylboronic acids (1.2 equiv.), in the presence of $Pd(PPh_3)_4$ (3 mol%) and K_2CO_3 (2.5 equiv.), in DMF, at 130 °C, for 10-12 hours afforded 2-aryl-4-(trifluoromethyl)-quinolines **10** in 41–97% yields (**Scheme 4.3, Table 4.3**).



9 **10**

Scheme 4.3: Synthesis of compounds **10**.

Reaction conditions: (*i*) substituted arylboronic acid (1.2 equiv.), $Pd(PPh_3)_4$ (2 mol%), K_2CO_3 (2.5 equiv.), DMF, 130 °C, 10 - 12 h.

Table 4.3. Synthesis of compounds **10**.

10	**R^1**	**R^2**	**Yield, (%)[a)]**
10a	H	2,3-$OCH_3C_6H_3$-	94
10b	H	2-OCH_3-5-FC_6H_3-	73
10c	H	3-FC_6H_4-	91
10d	H	4-$CF_3C_6H_4$-	41
10e	6-CH_3	2,3-$OCH_3C_6H_3$-	86
10f	6-CH_3	2,3-$OCH_3C_6H_3$-	95
10g	6-CH_3	2-OCH_3-5-FC_6H_3-	97
10h	6-CH_3	C_6H_5-	94
10i	6-CH_3	3-FC_6H_3-	95
10g	6-CH_3	4-FC_6H_3-	94

10k	6-F	2-$OCH_3C_6H_3$-	87
10l	6-F	2,3-$OCH_3C_6H_3$-	89
10m	6-F	2,5-$OCH_3C_6H_3$-	91
10n	6-F	4-FC_6H_3-	89

[a] Yield of isolated products

In the case of product **10d**, the lower yield can be explained by strong electron withdrawing effect of the trifluoromethyl group in *para*-position of the arylboronic acid.

The structures of all obtained compounds were characterized by ^{1}H, ^{13}C, ^{19}F NMR spectroscopy, IR spectral data as well as MS and HRMS methods. The structure of **10a** was independently confirmed by X-ray analysis (**Figure 11**). Torsion angle between quinoline core and aryl fragment lies within 41.97°–42.82°.

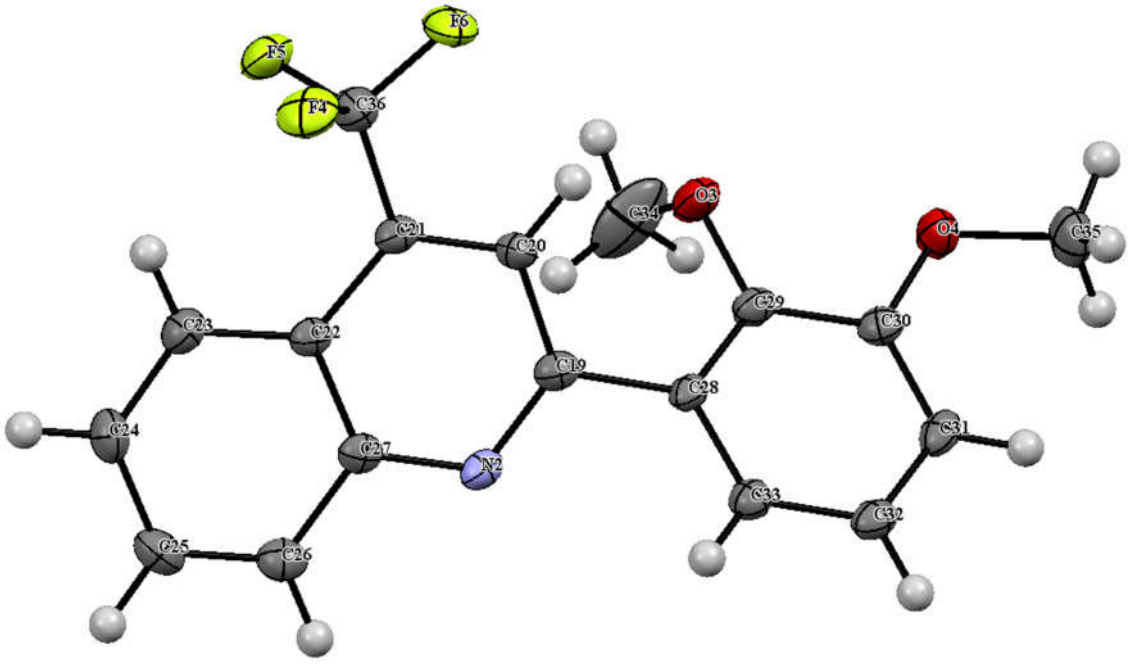
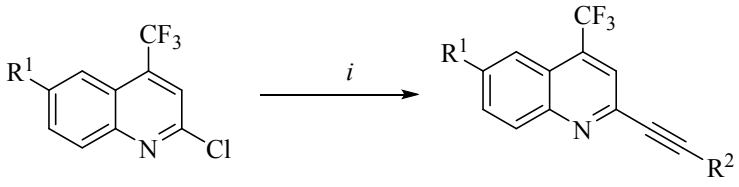


Figure 11. ORTEP of compound **10a** (50% probability level).

4.4 Sonogashira reaction of 2-chloro-4-(trifluoromethyl)quinolines

Continuing my research program dedicated to the design and synthesis of novel quinolines, the reaction of substituted 2-chloro-4-(trifluoromethyl)quinolines was

examined with a set of alkynes. I have chosen 2-chloro-4-(trifluoromethyl)quinolines as a key precursor due to its high reactivity of its chlorine at the position 2 towards nucleophiles in the presence of palladium catalyst (**Scheme 4.4**). Accordingly, 2-chloro-4-(trifluoromethyl)quinoline **9** was treated with terminal alkynes (R = alkyl, aryl) in THF in the presence of 2 mol% $Pd(PPh_3)_2Cl_2$, CuI (4 mol%), and triethylamine (3 equiv.) under an inert atmosphere. The reaction proceeded smoothly at room temperature to give 2-alkynyl-4-(trifluoromethyl)quinolines **11a-f** in good to excellent yields (see **Table 1.3**).



9 **11**

Scheme 4.4: Synthesis of compounds **11**.

Reaction conditions: (*i*) alkyne (1.2 equiv.), $Pd(PPh_3)_2Cl_2$ (2 mol%), CuI (4 mol%), Et_3N (3 equiv.), THF, 23 °C, 10 - 12 h.

Table 4.4. Synthesis of compounds **11**.

11	**R^1**	**R^2**	**Yield, (%)[a)]**
11a	H	4-$CH_3C_6H_4$-	91
11b	H	4-*t*-BuC_6H_4-	88
11c	CH_3	C_6H_5-	90
11d	CH_3	4-*t*-BuC_6H_4-	92
11e	CH_3	*n*-Pr-	82
11f	F	*n*-Bu-	80

[a)] Yield of isolated products.

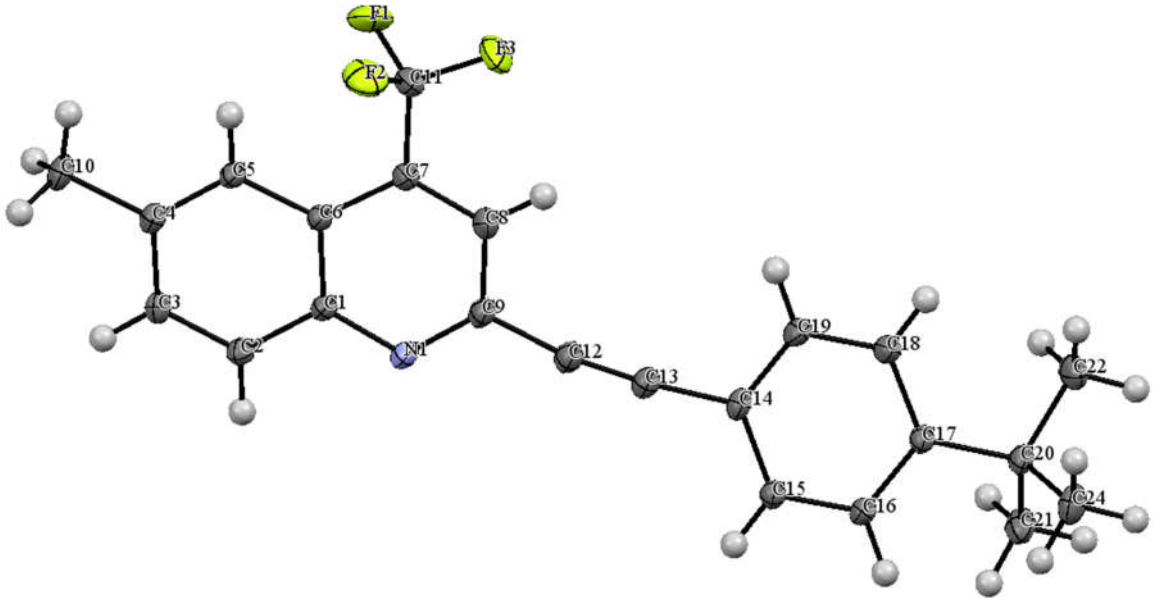


Figure 12. ORTEP of compound **11e** (50% probability level).

The structures of products were characterized by IR, ^{1}H, ^{13}C NMR spectra data as well as mass spectrometry analysis. Additionally, the structure of compound **11e** was independently confirmed by X-ray crystal structure analysis (**Figure 12**). The distance between acetylenic carbons C12-C13 is 1.204 Å, which is in good agreement with theoretical value – 1.2 Å.

4.5 Biological studies

Nucleotide pyrophosphatase/phosphodiesterase (NPP) is a class of dimeric enzymes that release nucleoside 5′-monophosphates from nucleotides and their derivatives and catalyze the hydrolysis of pyrophosphate and phosphodiester bonds (ATP, cyclic nucleotides, dinucleotide polyphosphates and nucleotide-sugars). NPPs can also generate nucleotides that activate purinergic receptors, which are responsible for mediate relaxation of gut smooth muscle as a response to the release of adenosine triphosphate (ATP).

There are seven known members of alkaline phosphatase (AP) superfamily, designated as NPP-1 to NPP-7. Interestingly, three of them – NPP1-3 – are involved in hydrolyzing nucleotides, NPP-6 and NPP-7 regulate break of phosphodiester bonds of

lysophospholipids or choline phosphodiesters. The role of NPP4 and NPP5 is yet to be identified.[95]

NPP-1 is found in bladder, heart, kidney, liver, lung and thymus. Furthermore, NPP-1 is the first to be demonstrated to have a unique role in regulating mineralization and is responsible for supplying the larger amount of inorganic pyrophosphate (PP_i). NPP-3 was detected in airway epithelium, in choroid plexus epithelial cells, hepatocytes, epithelial cells of the bile duct and human basophils.[96]

Both NPP-1 and NPP-3 are mainly present in the plasma membranes. For optimal activity, both NPP-1and NPP-3 require alkaline pH and presence of divalent ions, like zinc (Zn^{2+}) or magnesium (Mg^{2+}).[97]

4.5.1 Structure–activity relationship

The studies were accomplished at the Center for Advanced Drug Research, COMSATS Institute of Information Technology, Abbottabad, Pakistan, as a part of a cooperation project (research group of Prof. J. Iqbal).

2-Aryl-4-(trifluoromethyl)quinolines and differently substituted 2-(ethynyl)-4-(trifluoromethyl)-quinoline derivatives **10a–n** and **11a–f** were tested for their inhibitory activity towards nucleotide pyrophosphatase/phosphodiesterases h-NPP-1 and h-NPP-3.

Compounds, which exhibited inhibition of either h-NPP-1 or h-NPP-3 activity over 50% in the initial screening, were further evaluated for the determination of IC_{50} values. Variation of substituents on aromatic rings significantly affected the inhibitory potency and selectivity towards NPPs. As outlined in **Table 4.5.1** fluorinated quinolines exhibited IC_{50} values in the range of 0.095 ± 0.001 to 0.62 ± 0.02 µM and 0.041 ± 0.001 to 1.37 ± 0.11 µM for h-NPP-1 and h-NPP-3, respectively.

Among all, 2-(2,3-dimethoxyphenyl)-6-fluoro-4-(trifluoromethyl)quinoline **10l** was the lead candidate showing the highest inhibition of h-NPP-1 and h-NPP-3: an IC_{50} value of 0.095 ± 0.001 µM, which is 90-fold more potent compared to suramin (IC_{50} ± SEM = 8.67±1.30 µM), which was used as reference standard inhibitor and with an IC_{50} value of 0.041±0.001 µM, which is almost 31-fold more potent compared to suramin (IC_{50} ± SEM = 8.67 ± 1.30 µM), respectively.

Table 4.5.1 Nucleotide pyrophosphatase/phosphodiesterase (h-NPP-1 and h-NPP-3) activity of synthesized compounds at 0.01mM.

Compound	h-NPP-1 IC_{50} [a] (μM) ±SEM **(% inhibition)** [b]	h-NPP-3 IC_{50} [a] (μM) ±SEM **(% inhibition)** [b]
10a	38.1%	0.29±0.01
10b	41.8%	0.21±0.002
10c	0.24±0.002	0.084±0.001
10d	0.36±0.01	0.11±0.002
10e	21.4%	1.37±0.11
10h	0.27± 0.04	0.17±0.03
10i	48.6%	0.18±0.01
10j	39.2%	0.35±0.09
10k	0.31±0.03	0.55±0.03
10l	**0.095±0.001**	**0.041±0.001**
10m	36.1%	0.12±0.03
10n	0.34±0.03	0.16±0.02
11a	**0.13±0.01**	0.24±0.05
11b	0.38±0.01	0.84±0.09
11c	0.62±0.02	0.41±0.06

11d	38.2%	0.24±0.01
11e	0.44±0.01	0.23±0.03
11f	31.4%	**0.17±0.03**
Suramin **(Positive control)**	**8.67 ± 1.30**	**1.27 ± 0.08**

[a)] IC_{50} is the concentration at which 50% of the enzyme activity is inhibited. [b)] The % inhibition of the enzyme activity using 0.1 mM of the tested compound. The inhibitory concentrations are expressed as mean ± SEM, all experiments were carried out in triplicate.

Among compounds **11a-f** only four were active against h-NPP-1. Compound **11a** having IC_{50} ± SEM = 0.13±0.01 μM was found as the most potent inhibitor with the highest activity. Furthermore, compound **11f** showed highest selective activity against h-NPP-3 (inhibitory potential was found to be almost 7.5-fold higher than standard inhibitor – suramin (IC_{50} ± SEM = 1.27±0.08 μM)) and only partial inhibition against h-NPP-1.

4.6 Conclusions

I described a facile and efficient method for the preparation of 2-aryl-4-(trifluoromethyl)quinolines and 2-(arylethynyl)-4-(trifluoromethyl)quinolines by a one-step synthetic strategy starting from substituted 2-chloro-4-(trifluoromethyl)quinolines via Suzuki-Miyaura and Sonogashira protocols. Desired compounds were obtained with good yields. The scope and limitation of the method were extensively studied and the structures of two products were unambiguously confirmed by a single-crystal X-ray diffraction.

The biological evaluation of a set of prepared compounds showed high nucleotide pyrophosphatase/phosphodiesterase (h-NPP-1 and h-NPP-3) activity. Compound **10l** showed the highest activity against both h-NPP-1 and h-NPP-3 and is potential drug candidate.

5. Design and synthesis of novel 1,3-dialkyl-1,9-dihydro-2*H*-pyrimido[4,5-*b*]indole-2,4(3*H*)-diones

5.1 Introduction

Indole and its various derivatives are attracting attention because of their wide range of biological, medicinal activities, a frequent occurrence in natural products, and multiple uses in organic synthesis. [107]

Uracil with its derivatives plays an important role in the chemistry and the biology as the core constituents of the nucleic acids. In pharmaceutical chemistry, 1,3-dimethyl-6-aminouracil is known as a starting compound for the synthesis of theophylline-like xanthines.[98] 5-Fluorouracil is a known medication used to treat different types of cancer.[99]

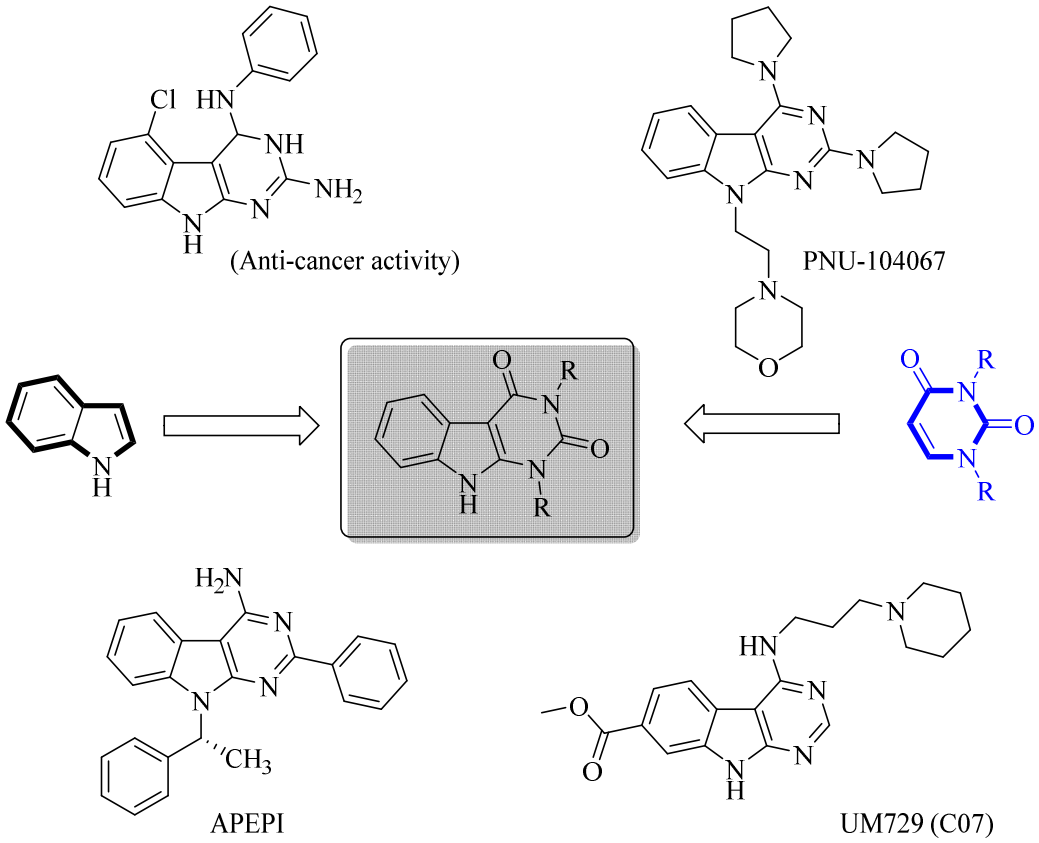


Figure 13. Examples of pyrimidoindole-based chemotherapeutic agents (drugs).

Moreover, pyrimido[4,5-*b*]indoles show remarkable biological significance and have therefore been used as key building blocks in the construction of medicinal and functional materials. For instance, a wide range of medicinal materials using pyrimidoindole building blocks showed anti-cancer,[100–103] anti-inflammatory, antihypertensive[104] and neuroprotective activity[105],[106–108]. In a recent study of Yao *et al.*, some pyrimidoindole derivatives were found to show agonistic effects on self-renewal of hematopoietic stem cells.[107] Sauvageau and colleagues discovered 9*H*-pyrimido[4,5-*b*]indol-4-amine (UM729) as new anti-leukemic drug through a cell-based assays and promising candidate in stem cell transplantation and gene therapy.[109] Recently, pyrimido[4,5-*b*]indol-4-amines and -2,4-diamines have been found to be new antiasthmatics and as agents against neurodegenerative disorders.[110],[111] In addition, Saito *et al.* have shown 9*H*-pyrimido[4,5-*b*]indoles can act as extended purine bases to form unnatural nucleosides and can be used as a very effective probe for the detection of DNA damage[112] (**Figure 13**).

The next step of my research was to combine both potential heterocyclic fragments of uracil and indole into pyrimido[4,5-*b*]indole. For this reason, the development of efficient synthetic methods in which both the indole and the uracil frameworks are combined simultaneously remains a challenging task.

To date, a number of synthetic strategies toward pyrimido[4,5-*b*]indoles have been developed (**Figure 14**). In most of the synthetic routes reported the functionalized indoles have been used as starting materials. For example:

- By condensations of 2-amino-3-(cyano/carboethoxy)-indoles with formic acid in presence of base provide desired compounds;[113,114]
- By cascade reactions of 1-bromo-2-(2,2- dibromovinyl)benzenes with aldehydes and aqueous ammonia;[115]
- By reaction of 2-ethoxy(3-benzylidene)indolenine tetrafluoroborate with amidines or guanidines;[116,117]
- By photolysis of 8-phenyltetrazolo[1,5-*c*]pyrimidines in trifluoroacetic acid;[118] photocyclization of 4-anilinotrichloropyrimidine;[119] or UV irradiation of 3-aryl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidines;[120]
- By palladium-catalyzed intramolecular arylation reaction of 4-aryloxy- or 4-anilino-5-iodopyrimidines;[121]
- Thermolysis of 6-azidouracils;[122]

- By reaction of *p*-benzoquinone with 1,3-dimethyl-6-aminouracil.[123]

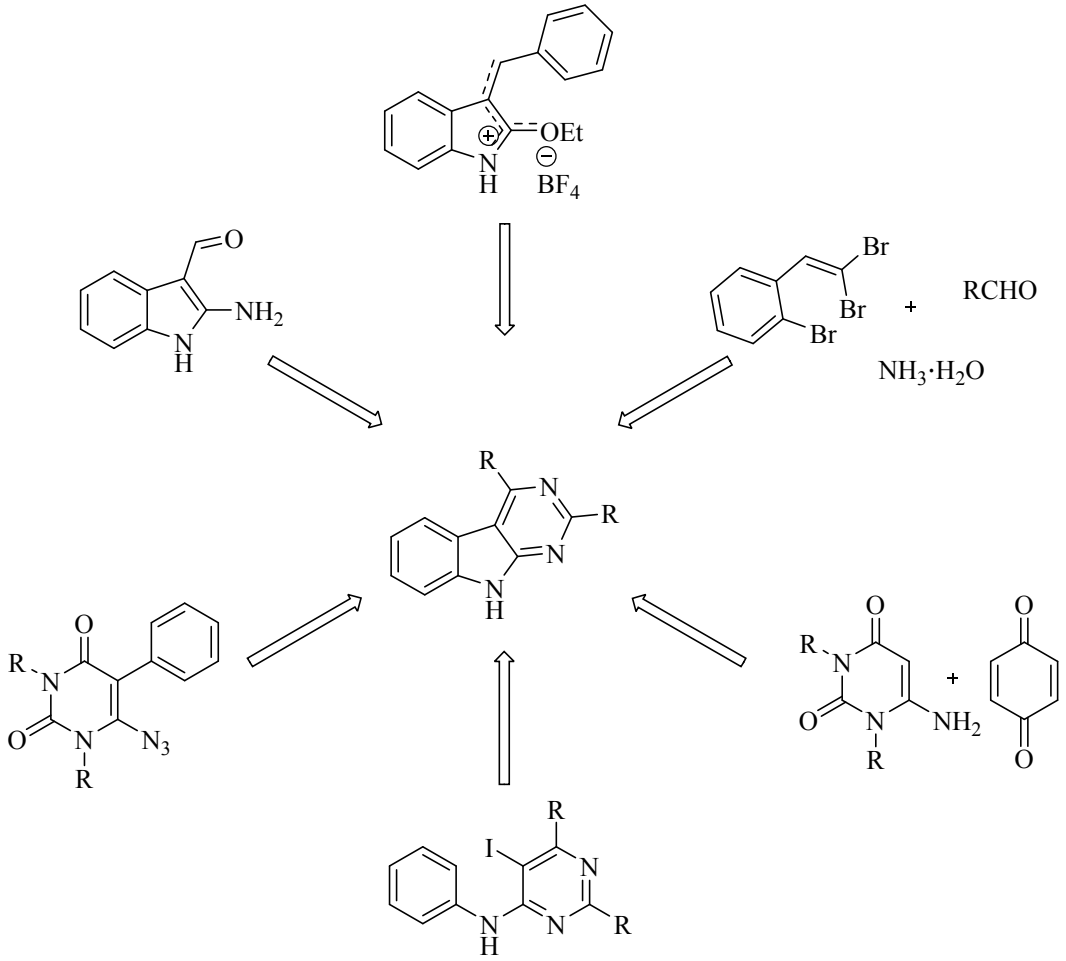


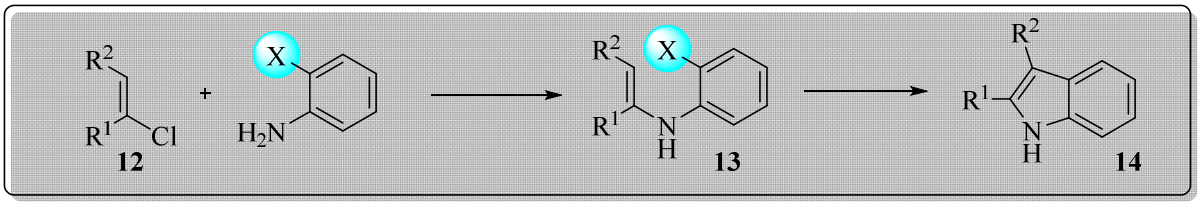
Figure 14. Known retrosynthetic disconnections to pyrimido[4,5-*b*]indoles.

While those pioneering methods are generally efficient and reliable, they usually start from substrates that already have an indole or uracil moiety. Furthermore, some of those syntheses require harsh reaction conditions and toxic or explosive reagents and multistep processes.

Nonetheless, interesting biological properties motivated me to find an efficient route to pyrimido[4,5-*b*]indoles. According to the aim of this project, I synthesized new condensed heterocycles, which are potentially interesting as pharmacologically active compounds.

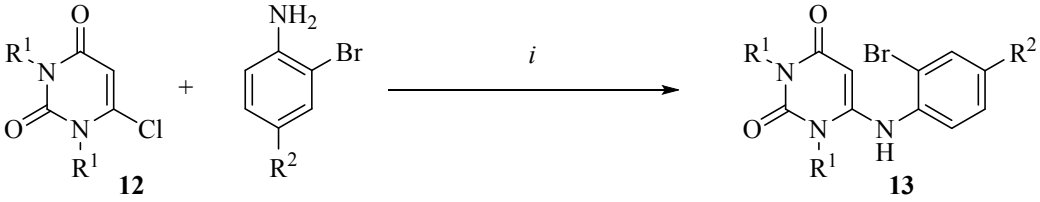
5.2 Synthesis of 6-(2-bromoarylamino)pyrimidine-2,4(1*H*,3*H*)-diones

This research is partially based on some previous works in Prof. Langer's group with deazaalloxazines.[124] My synthetic concept includes the consequent reaction of 6-chlorouracils with substituted 2-bromoanilines followed by an intramolecular cyclization of obtained anilinouraciles (**Scheme 5.2**).



Scheme 5.2. Schematic presentation of proposed transformation.

As a starting point, I synthesized 6-(2-bromoarylamino)-1,3-dialkylpyrimidine-2,4(1*H*,3*H*)-diones **13** by reaction of corresponding 6-chloro-1,3-dialkylpyrimidine-2,4(1*H*,3*H*)-dione **12** with anilines and *n*-butyl lithium (solution in hexanes) at -78 °C overnight according to the previous research[106] (**Scheme 5.2.1**). Thus, obtained products were further cyclized to desired pyrimidoindoles **13**.



Scheme 5.2.1. Synthesis of compounds **13**.

Reaction conditions: (*i*) *n*-BuLi (2.2 equiv.), THF, -78 °C – 20 °C, 10 h.

Table 5.2 Synthesis of compounds **12**.

13	**R^1**	**R^2**	**Yield, %**[a)]
13a	CH_3	H	78
13b	CH_3	CH_3	85
13c	CH_3	*i*-Pr	70
13d	CH_3	Cl	81

13e	CH_3	F	90
13f	Et	H	91
13g	Et	CH_3	92
13h	Et	*i*-Pr	90
13i	Et	Cl	67
13j	Et	F	85
13k	*n*-Pr	H	91
13l	*n*-Pr	CH_3	88
13m	*n*-Pr	*i*-Pr	80
13n	*n*-Pr	Cl	64
13o	*n*-Pr	F	91
13p	*n*-Bu	H	92
13q	*n*-Bu	CH_3	70
13r	*n*-Bu	Cl	90

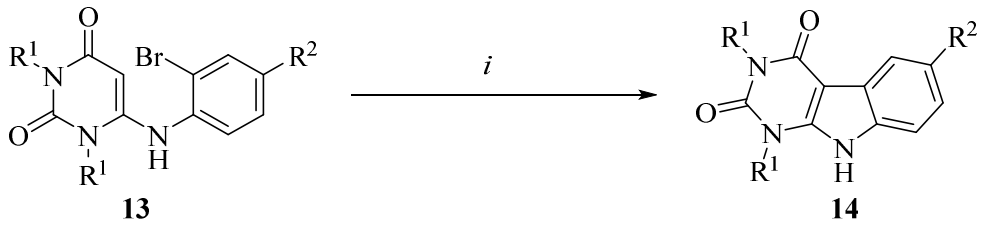
[a] Yield of isolated products.

In most of the cases, no additional purification of obtained compounds was required. The structures of synthesized compounds were established by NMR, IR spectroscopy methods, and mass spectrometry. In the ^{1}H NMR spectra of 2-bromoarylated aminouraciles, the singlets of N*H*-group appear at 4.9-5.1 ppm ($CDCl_3$). The proton signals of 5-C*H* bond of pyrimidine moiety appear at 6.1-6.5 ppm ($CDCl_3$).

5.3 Preparation of 1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-diones via intramolecular arylation reaction

With these results in hand, I next studied cyclization of 6-(2-bromoarylamino)-pyrimidine-2,4(1*H*,3*H*)-dione **13** into pyrimido[4,5-*b*]indoles **14**. The first attempt of

cyclization using $Pd(OAc)_2$ as palladium source, DBU (2.5equiv.) as a base in DMA at 130 °C, 4-5 h gave 85 % yield product (**Scheme 5.3**, **Table 5.3**). Raising the temperature to 145-150 °C accelerates the conversion, and the almost full consumption of starting materials was already detected during first 3-4 hours of reaction (TLC control).



Scheme 5.3. Synthesis of compounds **14**.

Reaction conditions: (*i*) $Pd(OAc)_2$ (5 mol%), $PCy_3 \cdot HBF_4$ (10 mol%), DBU (2.5 equiv.), DMA, 145 °C, 3-4 h.

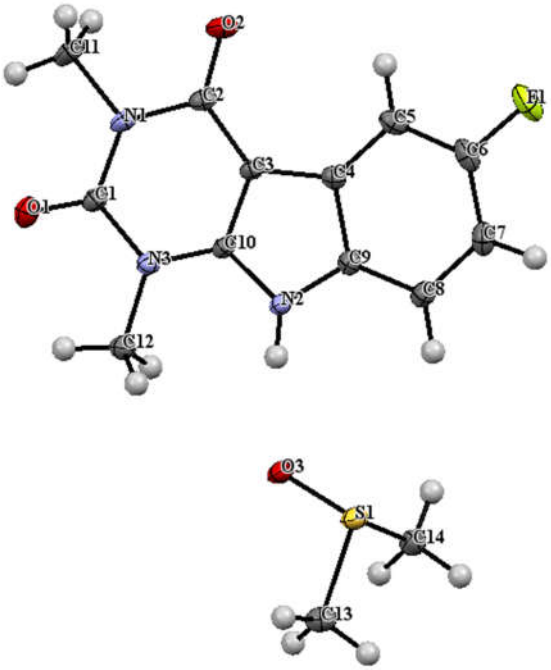
Table 5.3. Synthesis of compounds **14**.

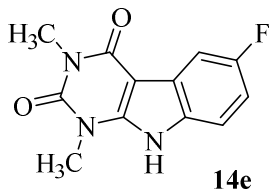
14	**R^1**	**R^2**	**Yield, %[a)]**
14a	CH_3	H	78
14b	CH_3	CH_3	89
14c	CH_3	*i*-Pr	88
14d	CH_3	Cl	90
14e	CH_3	F	90
14f	Et	H	91
14g	Et	CH_3	92
14h	Et	*i*-Pr	99
14i	Et	Cl	89
14j	Et	F	95
14k	*n*-Pr	H	89

14l	*n*-Pr	CH_3	87
14m	*n*-Pr	*i*-Pr	93
14n	*n*-Pr	Cl	71
14o	*n*-Pr	F	82
14p	*n*-Bu	H	83
14q	*n*-Bu	CH_3	87
14r	*n*-Bu	Cl	43

[a] Yield of isolated products.

The structures of products were characterized by IR, ^{1}H, ^{13}C NMR spectra data as well as MS and HRMS analysis. The structure of compound **14e** was independently confirmed by X-ray crystal structure analysis (**Figure 15**). A planar core of pyrimido[4,5-*b*]indole was observed.





14e

Figure 15. ORTEP of 6-fluoro-1,3-dimethyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione **14e** (50 % probability level). Crystal solvate with DMSO.

5.4 Conclusions

In this chapter, new efficient and convenient method for the synthesis of 1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-diones by intramolecular arylation reaction of 1,3-dialkyl-6-((2-bromo)arylamino)pyrimidine-2,4(1*H*,3*H*)-diones was developed.

Desired products obtained with good yields and might be of pharmacological interest.

6. Design and synthesis of novel *N*-substituted 1,8-dihydro-pyrrolo[2,3-*b*]indoles

6.1 Introduction

Indole is well known for its extensive presence in natural products, especially alkaloids. Many of them have been evolved as promising therapeutic agents due to their important biological activity against cancer, inflammation, and hypertension.[125]

Pyrroloindoles are a key structural fragment found in a wide number of biologically active natural compounds (**Figure 16**).

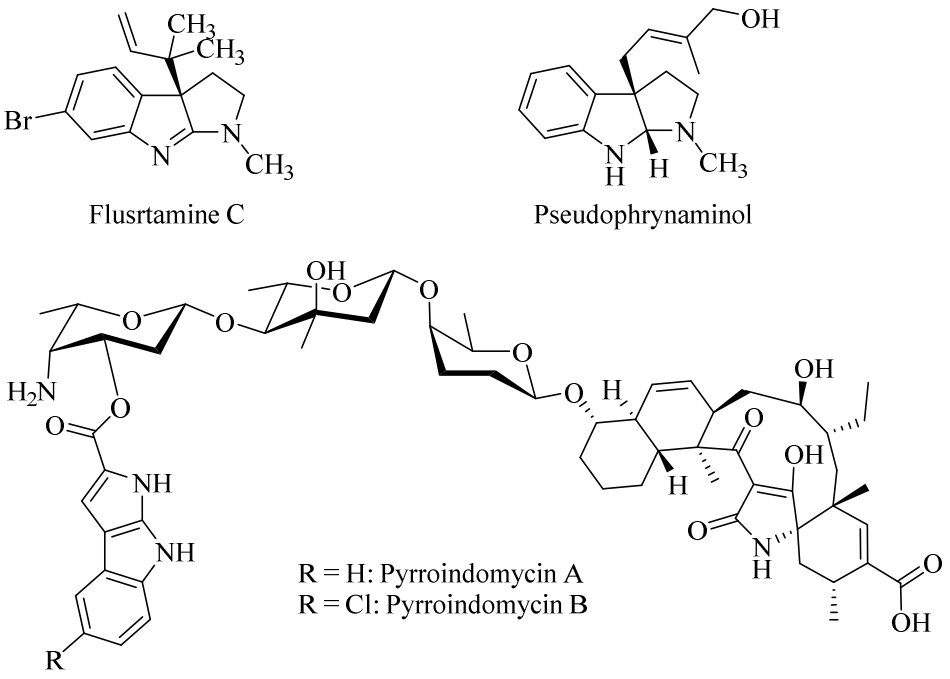


Figure 16. Representatives of pyroloindole family.

Pyrroindomycins (PYRs) are natural products, which were isolated during the screening of agents active against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium,* containing pyrroloindole fragment linked to tetronic acid core with macrocyclic ring.[126–133]

Tryptophan is presumed to be the precursor for the pyrroloindole moiety (**Figure 17**).

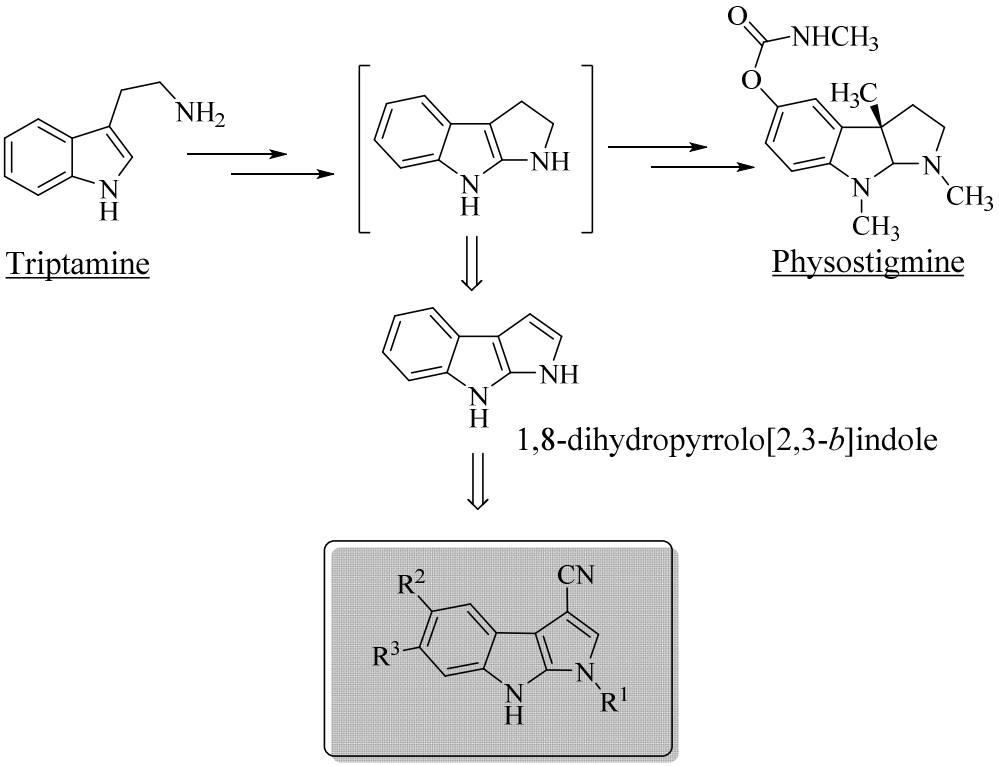


Figure 17. Structure relation between alkaloids and target compounds.

In 1864 Jobst and Hesse isolated alkaloid Physostigmine (also known as eserine) from the Calabar bean *Physostigma venenosum* growing in tropical forests of Africa.[134]

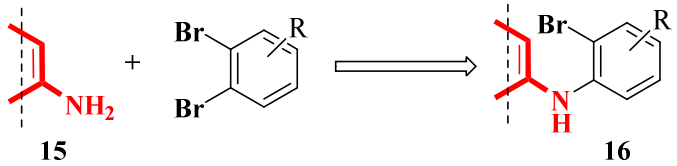
The first therapeutic use of physostigmine was in 1877 in the treatment of glaucoma. Notably, this is still one of its clinical uses. Physostigmine was the first discovered AChE inhibitor, which led to starting the practice of AChE inhibitors in clinical conditions.[135]

Physostigmine represents the first generation of cholinesterase inhibitors and has been a good model molecule for designing new derivatives with stronger cholinesterase inhibitory action. Having reversible inhibitory effect towards AChE, physostigmine has been used to treat myasthenia gravis, glaucoma, Alzheimer's disease[136] and atropine-induced coma.[137] Recently, Pal *et al*. proved indolo[2,3-*b*]indoles for the potential inhibition of yeast sirtuins, which are considered as promising targets for cancer therapeutics.[138]

As a result, numerous innovative methodologies toward the core hexahydro-pyrrolo[2,3-*b*]indole skeleton have been developed.[139–151]

It is an interesting challenge to find suitable synthetic routes to pyrroloindole core substances. The strategy I used, in this case, was the same I adopted in the synthesis of pyrimidoindoles (see Chapter 5) with slight modification (**Scheme 6.1**).

The first step is Buchwald-Hartwig amination reaction between 1-substituted 5-aminopyrrole-3-carbonitriles **15** and commercially available 1,2-dihalobenezenes (1,2-dibromobenzene, 2-bromo-4-chloro-1-iodobenzene and 1,2-dibromo-4,5-dimethoxybenzene).

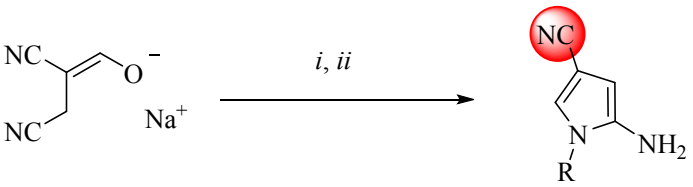


15 16

Scheme 6.1. Schematic presentation of proposed transformation.

In this sense, 5-amino-1-aryl/alkyl-1*H*-pyrrole-3-carbonitriles seemed to be the suitable starting materials for constructing [2,3]-fused indole derivatives. This precursor can be easily synthesized in two (or three, for aryl substituent) steps starting from cheap succinonitrile (**Scheme 6.1.1**). The properties of these compounds find expression as enamine moiety and good 1,3-binucleophile. The relative simplicity of the synthesis, structure similarity to the desired pyrrolo[2,3-*b*]indoles and great reactivity towards many reactions motivated me to use them.

Due to the instability of 1*H*-pyrrol-2-amines, in my research I used the N-substituted derivatives and in combination with the electron-withdrawing cyano functional group maintain their stability of electron-rich aminopyrrole ring.



Scheme 6.1.1. Preparation of precursors **15**.

Reaction conditions: (*i*) aliphatic or aromatic amine, EtOH-HOAc, (1:1 vol.), reflux, 45 min., (ii) NaOMe, methanol, 1 h.

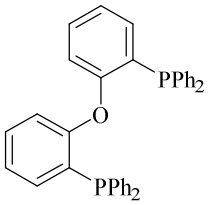
The second step in my research includes conducting of intramolecular cyclization in order to obtain target compounds.

6.2 Optimization of Buchwald-Hartwig reaction for synthesis of aminopyrroles

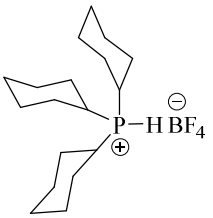
The Pd-catalyzed coupling of amines with aryl halides has become an important tool in the organic chemist's arsenal. In particular, the coupling of heteroaryl amines with aryl halides has been problematic. Over the past decades, with the development of new ligands became possible to dramatically enhance the rate of Buchwald-Hartwig reaction.

Initially, I attempted C–N bond-forming conditions using $Pd(OAc)_2$ as the catalyst source and screened four different ligands (±)-BINAP (entry 1), dppf (entry 2), DPEphos (entry 3), $PCy_3 \cdot HBF_4$ (entry 4) to compare both monodentate and bidentate ligands (**Figure 18**). I did not have success in obtaining any appreciable amount of desired coupling product in case of $PCy_3 \cdot HBF_4$, likely due to ineffective in current Buchwald-Hartwig reaction as long as the addition of Bu_4NBr for this particular substrate.

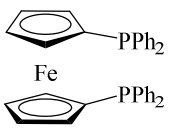
Optimization has shown the important role of bidentate ligands (DPEphos) in the step of approaching 5-arylaminopyrrole-3-carbonitriles.



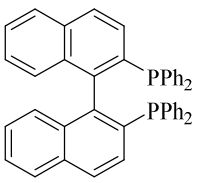
Bis[(2-diphenylphosphino)phenyl] ether **(DPEphos)**



Tricyclohexylphosphine tetrafluoroborate **($PCy_3 \cdot HBF_4$)**



1,1'- bis(diphenylphosphanyl) ferrocene **(dppf)**

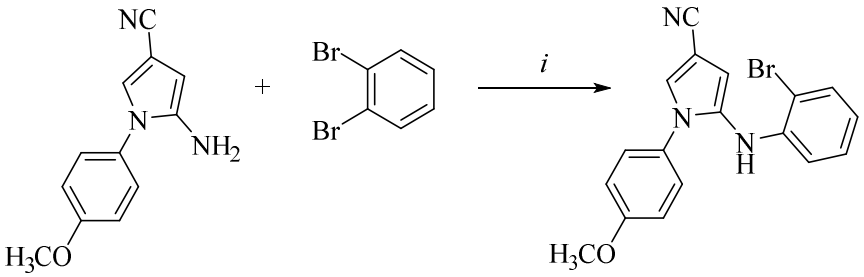


2,2'-bis(diphenylphosphino)-1,1'-binaphthyl **(BINAP)**

Figure 18. Selected examples of screened phosphine ligands.

The structure of the biaryl phosphine ligands is directly correlated to the efficiency of catalysts containing these ligands. The monodentate ligand showed to be ineffective in Buchwald-Hartwig reaction. Moreover, an increase of the product yield correlates with the increase of bite angle in the ligand row: BINAP (93°) – dppf (99°) – DPEphos (104°), which indicates the presence of angle effect.[152]

Changing to a more polar organic solvent like dioxane to help solubilize the base and further employing a strong base such as Cs_2CO_3 in combination with DPEphos (entry 7) did provide the requisite product, with a noticeable improvement in yield. Results of optimization are shown in **Table 6.2**.



Scheme 6.2 Optimization of target molecule **16.**

Reaction conditions: (*i*) $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), base (2.5 equiv.), solvent, 110 °C, 8-9 h.

Table 6.2. Optimization of C−N coupling reaction conditions.

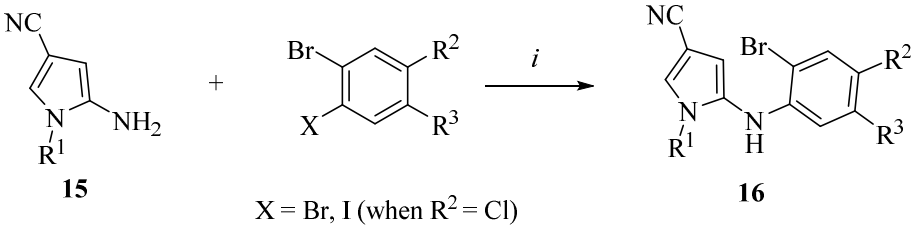
Entry	Solvent	Ligand/Additive	Base	Yield[a)]
1	toluene	Bu_4NBr	K_2CO_3	-[b)]
2	toluene	$PCy_3 \cdot HBF_4$	NaO*t*-Bu	-[b)]
3	toluene	(±)-BINAP	Cs_2CO_3	58
4	dioxane	(±)-BINAP	K_3PO_4	72
5	dioxane	dppf	Cs_2CO_3	85
6	dioxane	(±)-BINAP	Cs_2CO_3	80
7	**dioxane**	**DPEphos**	**Cs_2CO_3**	**92**

[a)] Yields of isolated products;

[b)] Product was not observed.

6.3 Synthesis of 5-((2-bromo)arylamino)-1*H*-pyrrole-3-carbonitriles

After the successful screening of the coupling conditions, I started synthesis of NH-arylated cyanopyrroles. Heating of the corresponding pyrrole with dihaloarene (1.2 equiv.), in the presence of $Pd(OAc)_2$ in an 5 mol% amount, DPEphos (10 mol%), and Cs_2CO_3 (2.5 equiv.) in toluene at 110 °C for 8 – 9 h afforded the desired 5-(2-bromophenylamino)-1*H*-pyrrole-3-carbonitriles **16** in 55–95% yield.



Scheme 6.3 Synthesis of compounds **16**.

Reaction conditions: (*i*) $Pd(OAc)_2$ (5 mol%), DPEphos (10 mol%), Cs_2CO_3 (2.5 equiv.), 1,4-dioxane, 110 °C, 8-9 h.

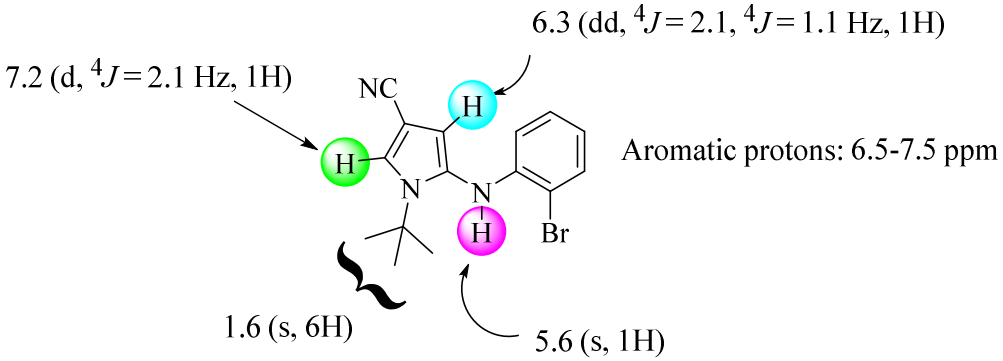
Table 6.3. Synthesis of compounds **16**.

16	R^1	R^2	R^3	Yield, %[a)]
16a	2,4,6-$CH_3C_6H_2$-	H	H	67
16b	2,4-$CH_3C_6H_3$-	H	H	90
16c	2,4-$CH_3C_6H_3$-	CH_3	CH_3	55
16d	2,4-$CH_3C_6H_3$-	Cl	H	70
16e	4-*i*-PrC_6H_4-	H	H	79
16f	4-*i*-PrC_6H_4-	Cl	H	72
16g	4-$OCH_3C_6H_4$-	H	H	92
16h	4-$OCH_3C_6H_4$-	Cl	H	72
16i	3-ClC_6H_4-	H	H	75

16j	3-ClC_6H_4-	Cl	H	63
16k	4-ClC_6H_4-	H	H	70
16l	4-ClC_6H_4-	Cl	H	75
16m	Bn-	H	H	60
16n	3,4-dimethoxyphenetyl-	OCH_3	OCH_3	68
16o	Cp-	H	H	50
16p	*n*-Pentyl-	H	H	76
16q	*t*-Bu-	OCH_3	OCH_3	68
16r	*t*-Bu-	H	H	85
16s	2,4,6-$CH_3C_6H_2$-	CH_3	CH_3	-*

a) Yield of isolated product.

The structures of synthesized compounds were confirmed by spectroscopic methods and mass spectrometry. In ^{1}H NMR spectra, the aromatic protons of pyrrole functionality appear at 7.0-7.2 ppm (solvent - $CDCl_3$) as doublets with a coupling constant ^4J ~ 1.9-2.1 Hz. Additionally, the broad singlets of N*H* group were detected at 5.5-6.1 ppm region.



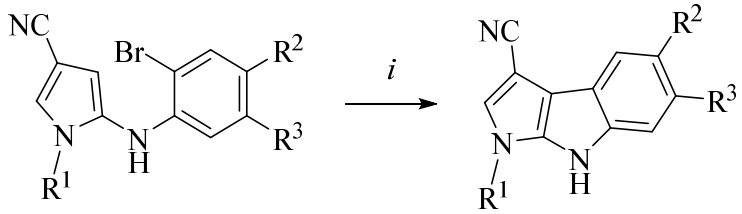
Scheme 6.3.1. ^{1}H NMR shifts of compound **16r** (in $CDCl_3$).

In addition, in the IR spectra, the typical strong intensive peaks of stretching vibrations of cyano group (-CN) were observed at ranges 2219-2228 cm^{-1}. All obtained

products were examined in the follow-up intramolecular arylation reaction to access 1,8-dihydropyrolo[2,3-*b*]indoles **17**.

6.4 Synthesis of 1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitriles

With this promising result, I next studied intramolecular cyclization reaction of previously obtained arylated aminopyrroles. Thus, the successful reaction of initial compounds **16** with $Pd(OAc)_2$ (5 mol%), $PCy_3 \cdot HBF_4$ (10 mol%) as phosphine ligand, DBU (2.5 equiv.) as a base in DMA at 145 °C for 3-4 hours afforded desired pyrrolo[2,3-*b*]indoles **17** in good yields (**Table 14**).



16 **17**

Scheme 6.4: Synthesis of 1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitriles **17**. *Reaction conditions*: (*i*) $Pd(OAc)_2$ (5 mol%), $PCy_3 \cdot HBF_4$ (10 mol%), DBU (2.5 equiv.), DMA, 145 °C, 3-4 h.

Table 6.4. Synthesis of compounds **17**.

17	**R^1**	**R^2**	**R^3**	**Yield, %[a)]**
17a	2,4,6-$CH_3C_6H_2$-	H	H	78
17b	2,4-$CH_3C_6H_3$-	H	H	85
17c	2,4-$CH_3C_6H_3$-	CH_3	CH_3	81
17d	2,4-$CH_3C_6H_3$-	Cl	H	75
17e	4-*i*-PrC_6H_4-	H	H	82
17f	4-*i*-PrC_6H_4-	Cl	H	80
17g	4-$OCH_3C_6H_4$-	H	H	60

17h	4-$OCH_3C_6H_4$-	Cl	H	87
17i	3-ClC_6H_4-	H	H	76
17j	3-ClC_6H_4-	Cl	H	72
17k	4-ClC_6H_4-	H	H	70
17l	4-ClC_6H_4-	Cl	H	56
17m	Bn-	H	H	62
17n	3,4-dimethoxyphenetyl-	H	H	60
17o	Cp-	H	H	65
17p	*n*-Pentyl-	H	H	53
17q	*t*-Bu-	OCH_3	OCH_3	45
17r	*t*-Bu-	H	H	70
17s	2,4,6-MeC_6H_2-	CH_3	CH_3	**39***

[a] Yield of isolated product.

The structures of newly synthesized compounds were elucidated by NMR methods, mass and IR spectroscopy. In ^{1}H NMR spectra of target materials, the signals of N*H*-proton of indole core were detected at 11.0-12.0 ppm region (DMSO-d_6).

Interestingly, the reaction of 5-amino-1-mesityl-1*H*-pyrrole-3-carbonitrile with 1,2-dibromo-4,5-dimethylbenzene gave not expected in this conditions product – 1-mesityl-5,6-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile **17s** in 39% yield. The structure of the product was independently confirmed by X-ray crystal structure analysis. Unfortunately, the data is not publishable, due to the bad quality of the small crystal. Nevertheless, the structure could be determined and gives the expected result (**Figure 19**).

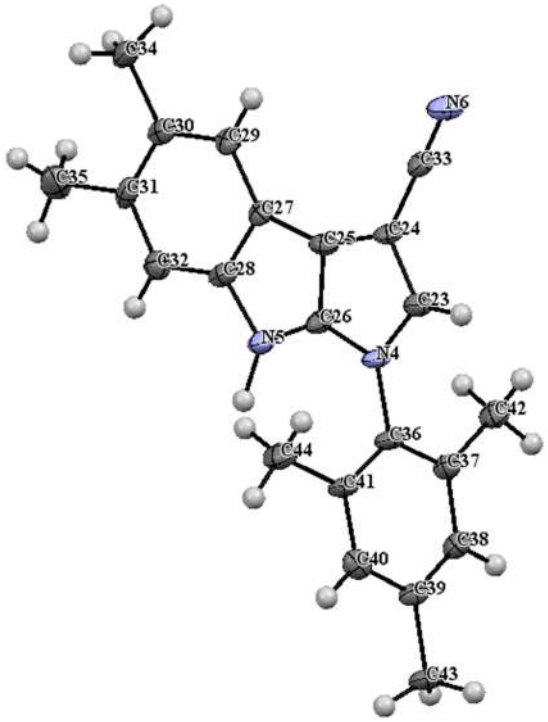
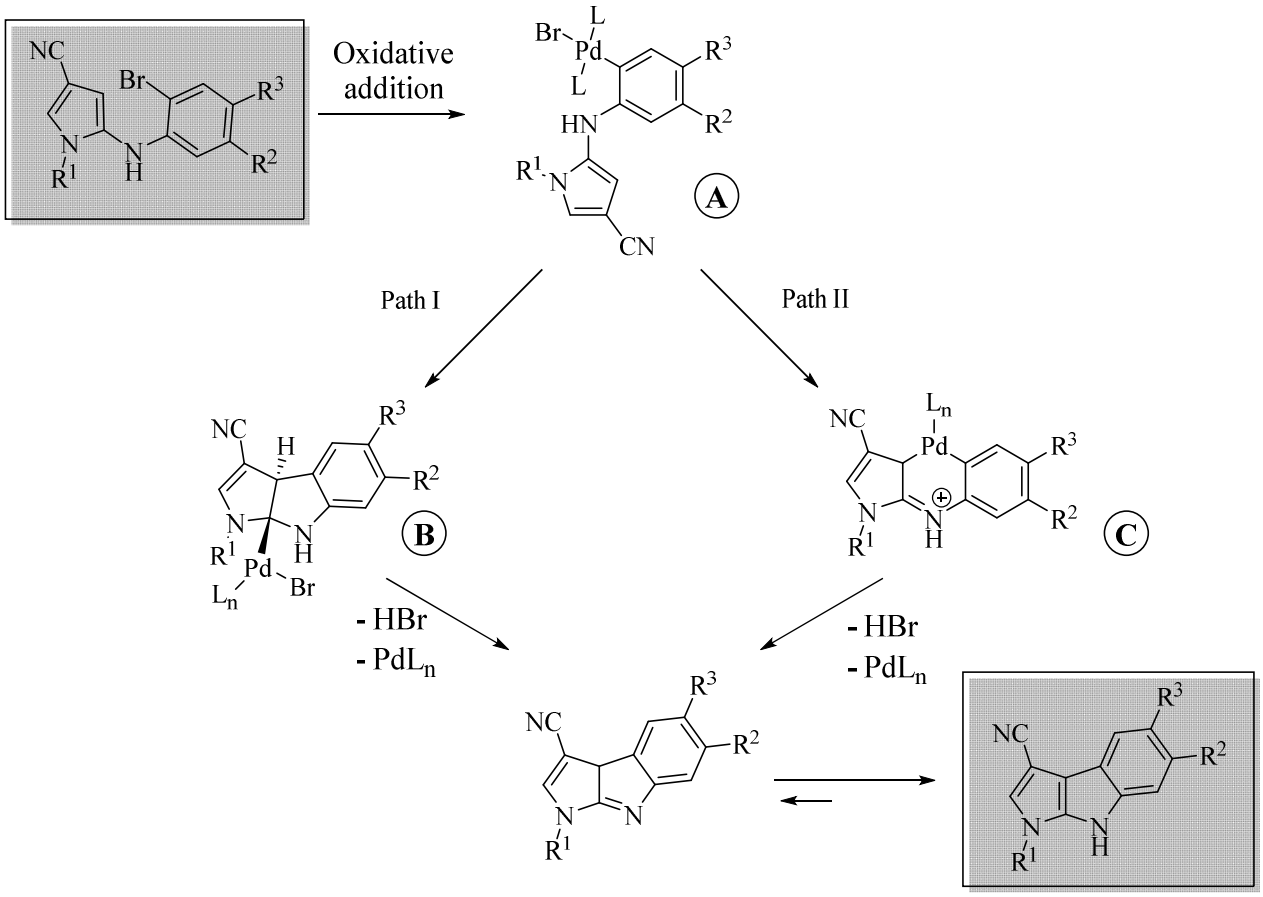


Figure 19. ORTEP of 1-mesityl-5,6-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile **17s** (50 % probability level).

With regards to the mechanism of cyclization, two possible pathways are depicted in **Scheme 6.4**.

Originally, oxidative addition generates species **A**, which can then either undergo a Heck-type process, through intermediate **B** or a catalytic dearomatization process via intermediate **C**. According to the previous studies of familiar reactions – electrophilic pathway preferred to Heck one, which seems less likely because of the high ring-strain of the trans-fused intermediate **B** which would be formed by the required *syn*-carbopalladation of the indole double bond.[153]



Scheme 6.4. Possible reaction mechanism of cyclization of **16** (ligands omitted for clarity).

6.5 Conclusion

In summary, I have demonstrated a novel synthesis of N-substituted pyrrolo[2,3-*b*]indole derivatives. The scope of the methodology was illustrated with the synthesis of biologically relevant N−H pyrroloindoles by employing 5-amino-3-cyanopyrroles as coupling partners in the sequential C−N and C−C bond-forming reactions.

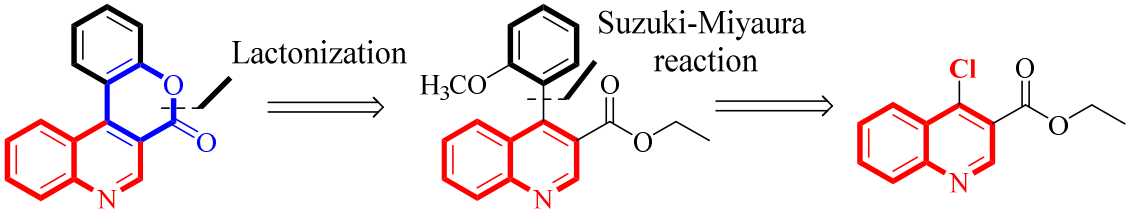
Furthermore, this methodology can be extended to the construction of other pyrrole-fused aromatic compounds.

7. Summary

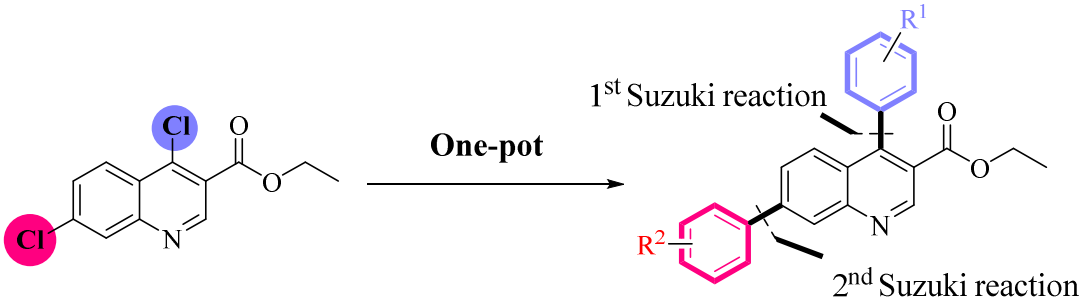
In the present thesis, a series of palladium-catalyzed reactions were utilized for the synthesis of novel heterocyclic compounds, especially quinolines and indole-like molecules.

Chapters 1 and **2** deal with Suzuki-Miyaura reaction protocols for the synthesis of various quinoline moieties.

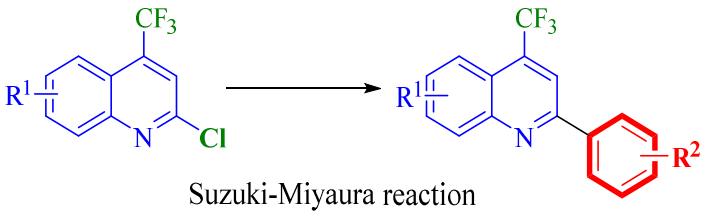
Simple reaction procedures were developed for the synthesis of novel 6*H*-chromeno[3,4-*c*]quinolin-6-ones.



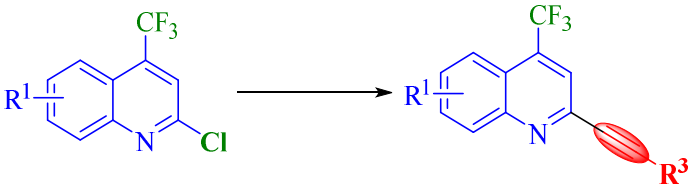
Site-selective one-pot cross-coupling was successfully applied to ethyl 4,7-dichloroquinoline carboxylates. The scope and limitations of the methodology along with some further transformations were studied.



In **Chapter 3**, a simple and efficient method for synthesis of arylated and alkynelated 4-trifluoroquinolines was developed along with results of biological evaluation of synthesized quinolines as nucleotide pyrophosphatase (NPPs) inhibitors.

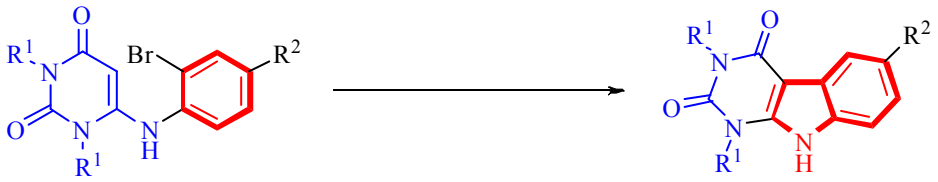


Suzuki-Miyaura reaction

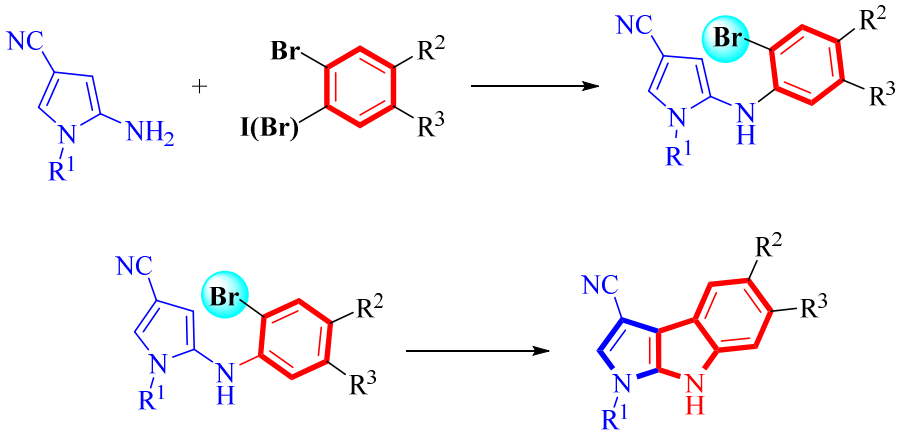


Sonogashira reaction

Preparative routes for the synthesis of novel 1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-diones were described in **Chapter 4**.



And finally, in **Chapter 5**, sequential Buchwald-Hartwig and intramolecular arylation reactions were successfully applied in the synthesis of various 1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitriles.



Supplement 1:

Experimental section

1.1 Analytics

^{1}H-NMR-Spectroscopy:

Bruker AVANCE 250 II (250 MHz), Bruker AVANCE 300 III (300 MHz), Bruker AVANCE 500 (500 MHz). The spectra were calibrated according to the solvent signals: 7.26 ppm for $CDCl_3$, 2.50 ppm for DMSO-d_6, 206.68 ppm for Acetone-d_6. Peak characterization: s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, h = heptet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets, m = multiplet.

^{13}C-NMR-Spectroscopy:

Bruker AVANCE 250 II (62.9 MHz), Bruker AVANCE 300 III (75.5 MHz), Bruker AVANCE 500 (125 MHz). The spectra were calibrated according to the solvent signals: 77.16 ppm for $CDCl_3$, 39.5 ppm for DMSO-d_6. Peak characterization: q = quartet, dd = doublet of doublets. DEPT method was used for determining the presence of primary, secondary, tertiary and quaternary carbon atoms.

^{19}F-NMR-Spectroscopy:

Bruker AVANCE 300 III (282 MHz).

All chemical shifts are given in ppm. All coupling constants *J* are indicated in Hz.

Mass spectrometry (MS):

GC 6890N/MSD 5973 (Agilent) or Finnigan MAT 95-XP (Thermo Electron).

High-resolution MS (HRMS):

Finnigan MAT 95 XP (Thermo Electron) (electron ionisation EI, 70 eV) or 6210 Time-of-Flight LC/MS (Agilent) (electrospray ionization, ESI). Only the measurements with an average deviation from the theoretical mass of ± 2 µDa were accounted as correct.

Infrared spectroscopy (IR):

Nicolet 380 FT-IR spectrometer with ATR sampling technique for solids as well as liquids. Abbreviations for signal allocations: w = weak, m = medium, s = strong.

X-ray crystallography:

Bruker-Nonius Apex X8 or Bruker Kappa Apex II diffractometers with CCD camera (Mo-Kα and graphite monochromator, λ = 0.71073 Å).

Melting point determination (mp):

Microscope Laborlux 12 Pol S, Mettler FP90 central Processor, SNT 12 V 100 K. The melting points are uncorrected.

Thin layer chromatography (TLC):

Merck silica gel 60 F_{254}. Detection under UV light at 254 nm and 366 nm without dipping reagent.

Column chromatography:

Chromatography was performed using Merck silica gel 60 (0.063-0.200 mm, 70-230 mesh). All solvents were distilled before use.

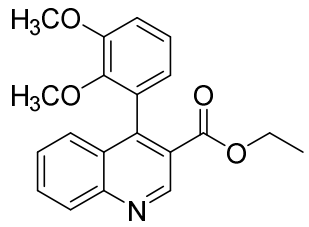
All chemicals and extra dry solvents were purchased from the standard chemical suppliers, such as Sigma-Aldrich®, Arcos®, Merck® and others. All reactions were monitored by TLC using UV light to visualize the course of the reaction.

General synthetic procedures and product characterization

General procedure for the synthesis of compounds 2a-x:

The mixture of corresponding ethyl 4-chloroquinoline-3-carboxylate (**1**), 1.2 equiv. of *ortho*-methoxyarylboronic acid, 5 mol % of $Pd(PPh_3)_4$ and 2.5 equiv. of K_2CO_3 was heated in dry DMF at 130 °C for 10-12 h under argon atmosphere. The solvent was evaporated in vacuo. The residue was purified by column chromatography (EA : Heptane = 1:5).

Ethyl 4-(2,3-dimethoxyphenyl)quinoline-3-carboxylate (2a):



Starting from ethyl 4-chloroquinoline-3-carboxylate (200 mg, 0.85 mmol), the product **2a** was isolated as yellow crystals (270 mg, 94 %); mp = 55 – 56 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 3.50 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.17 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.72 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, CH_{Ar}), 7.06 (dd, ^3J = 8.2 Hz, ^4J = 1.6 Hz, 1H, CH_{Ar}), 7.16 (dd, ^3J = 8.1 Hz, ^3J = 7.6 Hz, 1H, CH_{Ar}), 7.41 – 7.52 (m, 1H, CH_{Ar}), 7.59 (dd, ^3J = 8.5 Hz, ^4J = 0.9 Hz, 1H, CH_{Ar}), 7.77 (ddd, ^3J = 8.4 Hz, ^3J = 6.8 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 8.18 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 9.40 (s, 1H, CH_{Ar}).

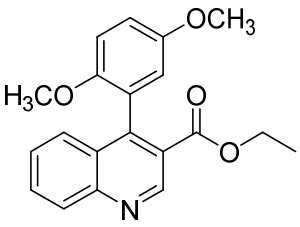
^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 56.0 (OCH_3), 60.6 (OCH_3), 61.2 (CH_2CH_3), 112.7 (CH), 122.0 (CH), 123.3(C), 123.9 (CH), 127.2 (C), 127.3 (CH), 127.7 (CH), 129.6 (CH), 131.1 (2*C, C+CH), 146.3 (C), 147.3 (C), 149.2 (C), 150.4 (CH), 152.8, 166.3 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2984 (w), 2962 (w), 2929 (w), 2840 (w), 1698 (s), 1601 (w), 1574 (m), 1505 (w), 1470 (s), 1456 (m), 1442 (m), 1426 (m), 1415 (m), 1369 (s), 1319 (m), 1301 (m), 1281 (m), 1259 (s), 1225 (s), 1166 (s), 1137 (m), 1124 (s), 1078 (s), 1012 (s), 960 (m), 941 (m), 869 (m), 815 (m), 790 (s), 770 (s), 755 (s), 684 (m), 676 (m), 644 (m), 604 (m), 587 (m), 562 (w), 535 (m);

MS (EI, 70eV): *m/z* (%) = 338 ($[M+H]^+$, 22), 337 (M^+, 100), 306 (21), 292 (18), 279 (14), 278 (71), 264 (14), 262 (15), 249 (13), 235 (20), 234 (18), 206 (19), 186 (36), 151 (14);

HRMS (EI): calcd. for $C_{20}H_{19}O_4N$ ([M]$^+$) 337.13086, found 337.13079.

Ethyl 4-(2,5-dimethoxyphenyl)quinoline-3-carboxylate (2b):



Starting from ethyl 4-chloroquinoline-3-carboxylate (200 mg, 0.85 mmol), the product **2b** was isolated as yellow crystals (255 mg, 89 %); mp = 96 – 97 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3). 3.62 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.18 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.71 (dd, ^4J = 2.8 Hz, J = 0.4 Hz, 1H, CH_{Ar}), 6.96 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 7.01 (dd, ^3J = 9.0 Hz, ^4J = 2.8 Hz, 1H, CH_{Ar}), 7.51 (ddd, ^3J = 8.3 Hz, ^3J = 6.8 Hz, ^4J = 1.2 Hz, 1H, CH_{Ar}), 7.63 (ddd, ^3J = 8.5 Hz, ^4J = 1.4 Hz, J = 0.5 Hz, 1H, CH_{Ar}), 7.80 (ddd, ^3J = 8.4 Hz, ^3J = 6.8 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 8.24 (d, ^3J = 8.4 Hz, 1H, CH_{Ar}), 9.40 (s, 1H, CH_{Ar}).

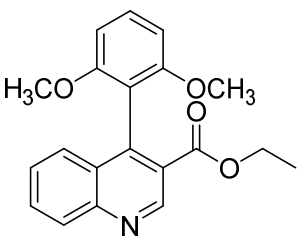
^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 56.0 (OCH_3), 56.3 (OCH_3), 61.3 (CH_2CH_3), 112.1 (CH), 114.6 (CH), 116.2 (CH), 123.7, 126.3, 127.4, 127.6 (CH), 127.7 (CH), 129.0 (CH), 130.5 (CH), 149.8 (2*C, C+CH), 151.0 (C), 153.6 (2*C), 166.0 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3335 (w), 3055 (w), 2997 (w), 2953 (w), 2932 (w), 2912 (w), 2834 (w), 1729 (s), 1718 (s), 1612 (w), 1573 (m), 1495 (s), 1463 (s), 1451 (m), 1440 (m), 1410 (m), 1374 (m), 1308 (m), 1281 (s), 1216 (s), 1178 (s), 1162 (s), 1138 (m), 1124 (m), 1101 (s), 1040 (s), 1030 (s), 1019 (s), 939 (m), 893 (m), 861 (m), 807 (s), 772 (s), 742 (s), 734 (s), 690 (s), 668 (s), 634 (m), 583 (m), 565 (m), 540 (m), 529 (m).

MS (EI, 70eV): *m/z* (%) = 338 (22), 337 ([M]$^+$, 100), 278 (38), 262 (16), 250 (17), 149 (11), 235 (14), 234 (14), 207 (13), 206 (16), 186 (12), 151 (12).

HRMS (EI): calcd. for $C_{20}H_{19}NO_4$ ([M]$^+$) 337.13086, found 337.13082.

Ethyl 4-(2,6-dimethoxyphenyl)quinoline-3-carboxylate (2c):



Starting from ethyl 4-chloroquinoline-3-carboxylate (150 mg, 0.64 mmol), the product **2c** was isolated as yellow crystals (93 mg, 43 %); mp = 139-140 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 3.61 (s, 6H, 2*OCH_3), 4.14 (q, ^3J = 7.1 Hz, 2H,

C*H*$_2$CH$_3$), 6.70 (d, ^3J = 8.4 Hz, 2H, CH$_{Ar}$), 7.42 (t, ^3J = 8.4 Hz, 1H, CH$_{Ar}$), 7.44 (ddd, ^3J = 6.8 Hz, ^4J = 1.4 Hz, 1H, CH$_{Ar}$), 7.53 (dd, ^3J = 8.6 Hz, ^4J = 1.6 Hz, 1H, CH$_{Ar}$), 7.74 (ddd, ^3J = 8.4 Hz, ^3J = 6.7 Hz, ^4J = 1.6 Hz, 1H, CH$_{Ar}$), 8.16 (d, ^3J = 8.6 Hz, 1H, CH$_{Ar}$), 9.43 (s, 1H, CH$_{Ar}$).

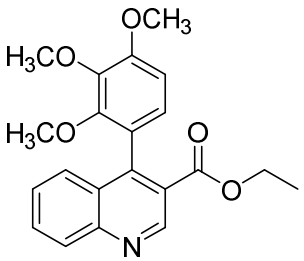
^{13}C NMR (63 MHz, CDCl$_3$): δ = 13.7 (CH$_2$*C*H$_3$), 55.8 (2*OCH$_3$), 60.8 (*C*H$_2$CH$_3$), 104.08 (2*CH), 114.2 (C), 124.1 (C), 126.9 (CH), 127.3 (CH), 127.5 (C), 129.6 (CH), 130.2 (CH), 130.8 (CH), 144.8 (2*C), 149.4 (C), 150.7 (CH), 157.5 (C), 166.4 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955 (w), 2926 (w), 2855 (w), 1726 (s), 1585 (m), 1503 (w), 1469 (s), 1430 (m), 1369 (m), 1298 (m), 1280 (s), 1252 (s), 1222 (s), 1212 (s), 1157 (s), 1104 (s), 1027 (s), 1018 (s), 983 (m), 955 (m), 925 (m), 860 (m), 828 (w), 805 (m), 782 (m), 771 (s), 761 (s), 741 (s), 678 (m), 608 (m), 564 (m), 531 (m);

MS (EI, 70eV): *m/z* (%) = 338 ([M+H]$^+$, 19), 337 ([M]$^+$, 79), 292 (23), 262 (18), 249 (26), 248 (20), 234 (22), 214 (12), 206 (21), 190 (13), 187 (12), 186 (95), 151 (13), 149 (21), 29 (29);

HRMS (EI): calcd for C$_{20}$H$_{19}$NO$_4$ ([M]$^+$) 337.13086, found 337.13041.

Ethyl 4-(2,3,4-trimethoxyphenyl)quinoline-3-carboxylate (2d):



Starting from ethyl 4-chloroquinoline-3-carboxylate (300 mg, 1.26 mmol), the product **2d** was isolated as yellow crystals (395 mg, 84 %); mp = 95 – 96 °C;

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.13 (t, ^3J = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 3.57 (s, 3H, OCH$_3$), 3.94 (s, 3H, OCH$_3$), 3.95 (s, 3H, OCH$_3$), 4.2 (q, ^3J = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 6.80 (s, 1H, CH$_{Ar}$), 6.81 (s, 1H, CH$_{Ar}$), 7.5 (ddd, ^3J = 8.4 Hz, ^3J = 6.8 Hz, ^4J = 1.3 Hz, 1H, CH$_{Ar}$), 7.7 (dd, ^3J = 8.6 Hz, ^3J = 0.8 Hz, 1H, CH$_{Ar}$), 7.8 (ddd, ^3J = 8.4 Hz, ^3J = 6.8 Hz, ^4J = 1.5 Hz, 1H, CH$_{Ar}$), 8.3 (d, ^3J = 8.4 Hz, 1H, CH$_{Ar}$), 9.4 (s, 1H, CH$_{Ar}$);

^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.9 (CH$_2$*C*H$_3$), 56.1 (OCH$_3$), 60.86 (OCH$_3$), 60.99 (OCH$_3$), 61.2 (*C*H$_2$CH$_3$), 107.1 (CH), 123.1 (C), 123.9 (C), 124.4 (CH), 127.5 (CH), 127.6 (CH), 127.7 (C), 129.3 (CH), 131.3 (CH), 142.3 (C), 147.5 (C), 148.7 (C), 150.0 (CH), 151.3 (C), 154.4 (C), 166.4 (C=O);

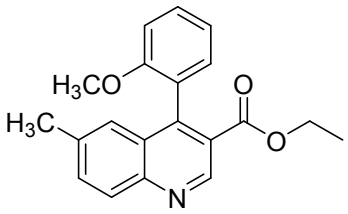
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2994 (w), 2969 (w), 2956 (m), 2935 (w), 2836 (m), 1724 (s), 1604 (m), 1573 (m), 1505 (w), 1488 (m), 1469 (m), 1462 (m), 1443 (m), 1434 (m), 1416 (m), 1381 (m), 1367 (m), 1291 (m), 1271 (m), 1263 (m), 1223 (s), 1198 (s), 1167 (m), 1151 (s), 1134 (m), 1120 (m), 1098 (s), 1056 (s), 1015 (s), 993 (s), 944 (m), 912

(m), 878 (m), 856 (m), 809 (s), 796 (s), 782 (s), 765 (s), 679 (m), 666 (m), 621 (m), 300 (m), 581 (m), 535 (m);

MS (EI, 70eV): *m/z* (%) = 368 ($[M+H]^+$, 23), 367 (M^+, 100), 322 (10), 308 (26), 292 (23), 264 (24), 221 (12), 186 (27);

HRMS (EI): calcd. for $C_{21}H_{21}O_5N$ ($[M]^+$) 367.14142, found 367.14122.

Ethyl 4-(2-methoxyphenyl)-6-methylquinoline-3-carboxylate (2e):



Starting from ethyl 4-chloro-6-methylquinoline-3-carboxylate (200 mg, 0.8 mmol), the product **2e** was isolated as yellow crystals (211 mg, 82 %); mp = 123 – 124 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 2.42 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 4.13 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 7.04 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 7.06 – 7.14 (m, 2H, CH_{Ar}), 7.31 (s, 1H, CH_{Ar}), 7.47 (ddd, ^3J = 8.2 Hz, ^3J = 6.2 Hz, ^4J = 3.0 Hz, 1H, CH_{Ar}), 7.59 (dd, ^3J = 8.6 Hz, ^4J =1.8 Hz, 1H, CH_{Ar}), 8.06 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 9.31 (s, 1H, CH_{Ar}).

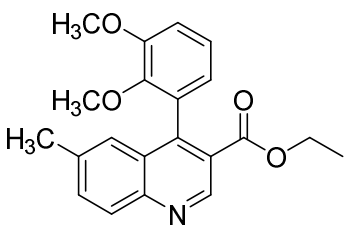
^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 21.9 (CH_3), 55.70 (OCH_3), 61.0 (CH_2CH_3), 110.9 (CH), 120.5 (CH), 123.7 (C), 125.8 (C), 126.2 (CH), 127.3 (C), 129.4 (CH), 129.8 (CH), 130.3 (CH), 133.3 (CH), 137.2 (C), 146.5 (C), 148.1 (C), 149.5 (CH), 156.8 (C), 166.7 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3049 (w), 3004 (w), 2983 (w), 2961 (w), 2937 (w), 2923 (w), 2899 (w), 2839 (w), 1939 (w), 1870 (w), 1702 (s), 1601 (s), 1570 (s), 1494 (s), 1461 (s), 1453 (s), 1437 (s), 1422 (s), 1365 (s), 1316 (s), 1287 (s), 1257 (s), 1236 (s), 1216 (s), 1177 (s), 1123 (s), 1106 (s), 1049 (s), 1024 (s), 1012 (s), 975 (m), 964 (m), 937 (m), 895 (w), 867 (m), 845 (m), 832 (s), 784 (m), 756 (s), 729 (s), 708 (m), 680 (m), 632 (m), 619 (s), 599 (m), 565 (m), 545 (m);

MS (GC, 70 eV) *m/z* (%): 321 ($[M]^+$, 90), 290 (19), 277 (10), 276 (50), 275 (11), 263 (12), 262 (63), 261 (11), 248 (27), 247 (11), 246 (26), 234 (17), 233 (60), 232 (410, 218 (12), 216 (11), 205 (13), 204 (24), 203 (14), 201 (17), 200 (100), 190 (11), 189 (10), 178 (11), 177 (12), 176 (18), 29 (36);

HRMS (ESI): calcd. for $C_{20}H_{19}NO_3$ ($[M]^+$) 321.13594, found 321.13575.

Ethyl 4-(2,3-dimethoxyphenyl)-6-methylquinoline-3-carboxylate (2f):



Starting from ethyl 4-chloro-6-methylquinoline-3-carboxylate (200 mg, 0.8 mmol), the product **2f** was isolated as yellow crystals (267 mg, 94 %); mp = 103 - 104°C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3). 2.43 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.17 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.70 (d, ^4J = 2.7 Hz, 1H, CH_{Ar}), 6.99-7.04 (m, 2H, CH_{Ar}), 7.35 (s, 1H, CH_{Ar}), 7.60 (dd, ^3J = 8.6 Hz, ^4J = 1.9 Hz, 1H, CH_{Ar}), 8.07 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 9.31 (s, 1H, CH_{Ar}).

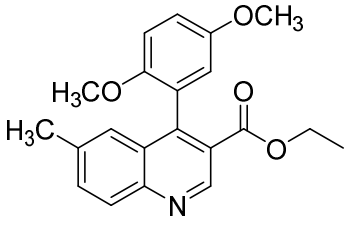
^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 21.8 (CH_3), 55.8 (OCH_3), 56.2 (OCH_3), 61.0 (CH_2CH_3), 112.2 (CH), 114.3 (CH), 116.2 (CH), 123.6 (C), 126.2 (CH), 126.7 (C), 127.2 (C), 129.2 (CH), 133.5 (CH), 137.4 (C), 146.5 (C), 147.8 (C), 149.3 (CH), 151.1, 153.6 (C), 166.4 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3064 (w), 3032 (w), 2991 (w), 2974 (w), 2944 (w), 2927 (w), 2904 (w), 2830 (w), 1727 (s), 1619 (w), 1586 (w), 1569 (m), 1497 (s), 1457 (s), 1440 (m), 1421 (s), 1389(w), 1366 (m), 1356 (m), 1300 (m), 1283 (s), 1272 (s), 1259 (s), 1236 (s), 1222 (s), 1203 (s), 1177 (s), 1146 (s), 1130 (s), 1101 (s), 1055 (s), 1034 (s), 1021 (s), 932 (m), 923 (m), 903 (m), 883 (m), 870 (m), 837 (s), 809 (s), 763 (s), 751 (s), 725 (s), 699 (s), 680 (m), 640 (m), 628 (m), 606 (m), 592 (m), 556 (m), 535 (m);

MS (GC, 70 eV) *m/z* (%): 351 ($[M]^+$, 100), 292 (38), 276 (13), 264 (14), 263 (13), 249 (10), 248 (11), 220 (13), 200 (12), 29 (22);

HRMS (ESI): calcd. for $C_{21}H_{21}NO_4$ ($[M+H]^+$) 352.15474, found 352.15433.

Ethyl 4-(2,5-dimethoxyphenyl)-6-methylquinoline-3-carboxylate (2g):



Starting from ethyl 4-chloro-6-methylquinoline-3-carboxylate (200 mg, 0.8 mmol), the product **2g** was isolated as yellow crystals (268 mg, 95 %); mp = 95-96°C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 2.42 (s, 3H, CH_3), 3.51 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.17 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.71 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, CH_{Ar}), 7.07 (dd, ^3J = 8.2 Hz, ^4J = 1.6 Hz, 1H, CH_{Ar}), 7.17 (dd, ^3J = 8.2 Hz, ^3J = 7.6 Hz, 1H, CH_{Ar}), 7.31 (s, 1H, CH_{Ar}), 7.60 (dd, ^3J = 8.6 Hz, ^4J = 1.9 Hz, 1H, CH_{Ar}), 8.08 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 9.33 (s, 1H, CH_{Ar}).

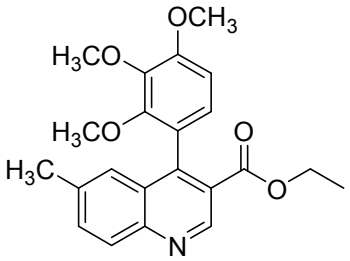
^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 22.0 (CH_3), 55.9 (OCH_3), 60.6 (OCH_3), 61.2 (CH_2CH_3), 112.6 (CH), 122.0 (CH), 123.4 (C), 123.9 (CH), 126.3 (CH), 127.2 (C), 129.1 (CH), 131.2 (C), 133.6 (CH), 137.5 (C), 146.3 (C), 146.8 (C), 147.6 (C), 149.3 (CH), 152.8 (C), 166.4 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3070 (w), 3045 (w), 3016 (w), 2993 (w), 2968 (w), 2939 (w), 2918 (w), 2874 (w), 2838 (w), 2827 (w), 1708 (s), 1623 (w), 1600 (w), 1574 (s), 1504 (w), 1470 (s), 1452 (s), 1422 (s), 1383 (w), 1358 (s), 1315 (s), 1297 (s), 1258 (s), 1223 (s), 1176 (s), 1143 (m), 1126 (s), 1113 (s), 1074 (s), 996 (s), 943 (m), 887 (w), 866 (w), 830 (s), 819 (m), 788 (s), 774 (s), 755 (s), 688 (m), 676 (m), 648 (s), 611 (m), 602 (m), 570 (m), 538 (m);

MS (GC, 70 eV) *m/z* (%): 351 ($[M]^+$, 100), 320 (24), 306 (21), 293 (18), 292 (73), 291 (10), 278 (16), 276 (19), 264 (11), 263 (16), 262 (11), 249 (17), 248 (18), 220 (22), 200 (44), 191 (150, 190 (13), 165 (11), 29 (35);

HRMS (EI): calcd. for $C_{21}H_{21}NO_4$ ($[M]^+$) 351.14651, found 351.14591.

Ethyl 6-methyl-4-(2,3,4-trimethoxyphenyl)quinoline-3-carboxylate (2h):



Starting from ethyl 4-chloro-6-methylquinoline-3-carboxylate (100 mg, 0.4 mmol), the product **2h** was isolated as yellow crystals (84 mg, 55 %); mp = 97 – 98 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 2.44 (s, 3H, CH_3), 3.56 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.17 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.78 (s, 2H, CH_{Ar}), 7.35 (s, 1H, CH_{Ar}), 7.61 (dd, ^3J = 8.6 Hz, ^4J =1.8 Hz, 1H, CH_{Ar}), 8.07 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 9.29 (s, 1H, CH_{Ar}).

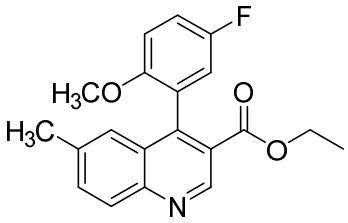
^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 22.0 (CH_3), 56.2 (OCH_3), 60.95 (OCH_3), 61.1 (OCH_3), 61.2 (CH_2CH_3), 107.1 (CH), 123.4 (C), 123.9 (C), 124.4 (CH), 126.2 (CH), 127.6 (C), 129.25 (CH), 133.4 (CH), 137.4 (C), 142.25 (C), 146.35 (C), 147.8 (C), 149.3 (CH), 151.3 (C), 154.2 (C), 166.7 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2996 (w), 2961 (w), 2936 (w), 2838 (w), 1873 (w), 1719 (s), 1599 (m), 1571 (m), 1491 (s), 1466 (s), 1441 (s), 1412 (s), 1390 (m), 1365 (s), 1295 (s), 1268 (s), 1228 (s), 1196 (s), 1181 (s), 1121 (s), 1093 (s), 1056 (s), 1031 (s), 1012 (s), 993 (s), 937 (m), 920 (m), 893 (m), 865 (m), 835 (s), 820 (s), 806 (m), 795 (m), 784 (m), 776 (m), 764 (s), 728 (m), 678 (m), 627 (m), 588 (m), 532 (m);

MS (GC, 70 eV) *m/z* (%): 382 (28), 381 ([M]$^+$, 100), 336 (11), 322 (28), 278 (24), 235 (13), 200 (30), 29 (29);

HRMS (EI): calcd. for $C_{22}H_{23}NO_5$ ([M]$^+$) 381.15707, found 381.15688.

Ethyl 4-(5-fluoro-2-methoxyphenyl)-6-methylquinoline-3-carboxylate (2i):



Starting from ethyl 4-chloro-6-methylquinoline-3-carboxylate (200 mg, 0.8 mmol), the product **2i** was isolated as yellow crystals (239mg, 88 %); mp = 132-133 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 2.45 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 4.17 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.88 (dd, ^3J = 8.4 Hz, ^3J = 3.1 Hz, 1H, CH_{Ar}), 6.97 (dd, ^3J = 9.1 Hz, ^3J = 4.3 Hz, 1H, CH_{Ar}), 7.17 (ddd, ^3J = 9.0 Hz, ^3J = 8.0 Hz, ^3J = 3.1 Hz, 1H, CH_{Ar}), 7.29 – 7.3 (m, 1H, CH_{Ar}), 7.62 (dd, ^3J = 8.6 Hz, ^3J = 2.0 Hz, 1H, CH_{Ar}), 8.08 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 9.33 (s, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 21.85 (CH_3), 56.2 (OCH_3), 61.1 (CH_2CH_3), 111.75 (d, $^3J_{C\text{-}F}$ = 8.3 Hz, CH), 115.6 (d, $^2J_{C\text{-}F}$ = 22.6 Hz, CH), 117.1 (d, $^2J_{C\text{-}F}$ = 24.2 Hz, CH), 123.3 (C), 125.7 (CH), 126.9 (C), 126.95 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 129.0 (CH), 133.6 (CH), 137.6 (C), 147.6 (C), 149.1 (CH), 152.9 (d, $^4J_{C\text{-}F}$ = 2.2 Hz), 156.77 (d, $^1J_{C\text{-}F}$ = 239.6 Hz), 165.9 (C=O). One Carbon signal cannot be detected.

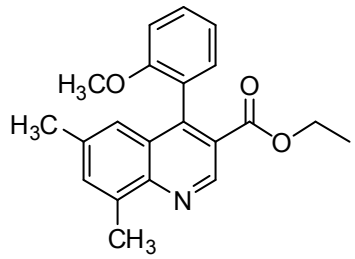
^{19}F NMR (282 MHz, $CDCl_3$): δ = -123.98 (CF).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3071 (w), 3030 (w), 2953 (w), 2922 (w), 2856 (w), 2833 (w), 2055 (w), 1889 (w), 1830 (w), 1727 (s), 1616 (w), 1596 (w), 1570 (m), 1495 (s), 1478 (m), 1464 (s), 1427 (m), 1390 (w), 1371 (m), 1361 (w), 1297 (s), 1272 (s), 1254 (s), 1241 (s), 1201 (s), 1177 (s), 1126 (s), 1097 (s), 1071 (s), 1030 (s), 1007 (m), 963 (m), 947 (m), 904 (m), 879 (m), 866 (m), 829 (s), 809 (s), 798 (s), 763 (s), 747 (s), 737 (s), 725 (s), 696 (s), 679 (w), 633 (m), 624 (m), 591 (m), 547 (m), 534 (m);

MS (GC, 70 eV) *m/z* (%): 339 ([M]$^+$, 100), 308 (23), 295 (11), 294 (45), 281 (18), 280 (89), 279 (13), 266 (35), 265 (15), 264 (28), 252 (21), 251 (62), 250 (48), 249 (11), 236 (15), 234 (12), 223 (11), 222 (20), 221 (13), 200 (72), 195 (10), 194 (11), 29 (47);

HRMS (ESI): calcd. for $C_{20}H_{18}FNO_3$ ([M+H]$^+$) 340.13435, found 340.13456.

Ethyl 4-(2-methoxyphenyl)-6,8-dimethylquinoline-3-carboxylate (2j):



Starting from ethyl 4-chloro-6,8-dimethylquinoline-3-carboxylate (200 mg, 0.76 mmol), the product **2j** was isolated as light yellowish liquid (153 mg, 60 %);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, ^{3}J = 7.1 Hz, 3H, CH_2CH_3), 2.37 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 4.13 (q, ^{3}J = 7.1 Hz, 2H, CH_2CH_3), 7.03 (d, ^{3}J = 8.2 Hz, 1H, CH_{Ar}), 7.07 – 7.11 (m, 2H, CH_{Ar}), 7.16 (s, 1H, CH_{Ar}), 7.41 – 7.53 (m, 2H, CH_{Ar}), 9.35 (s, 1H, CH_{Ar}).

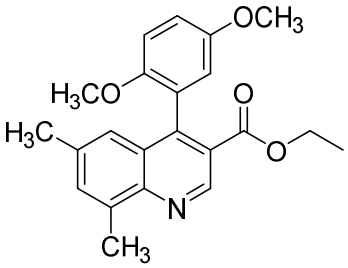
^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 18.4 (CH_3), 21.9 (CH_3), 55.7 (OCH_3), 61.0 (CH_2CH_3), 110.9 (CH), 120.5 (CH), 123.5 (C), 124.2 (CH), 126.2 (C), 127.4 (C), 129.7 (CH), 130.3 (CH), 133.7 (2*C, C+CH), 136.8 (C), 146.87 (C), 146.92 (C), 148.2 (CH), 156.8 (C), 166.7 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3976 (w), 2954 (w), 2923 (w), 2835 (w), 1707 (s), 1620 (w), 1601 (m), 1580 (m), 1488 (s), 1456 (m), 1433 (m), 1407 (m), 1366 (m), 1318 (s), 1291 (m), 1250 (s), 1196 (s), 1160 (s), 1141 (s), 1117 (s), 1062 (m), 1044 (m), 1023 (s), 937 (m), 859 (m), 826 (m), 815 (m), 750 (s), 725 (m), 687 (m), 655 (m), 623 (m), 567 (w);

MS (GC, 70 eV) *m/z* (%): 336 (25), 335 ($[M]^+$, 100), 290 (12), 276 (15), 262 (14), 247 (15), 246 (13), 232 (15), 214 (12), 29 (43);

HRMS (EI): calcd. for $C_{21}H_{21}N_3O_3$ ($[M]^+$) 335.15160, found 335.15138.

Ethyl 4-(2,5-dimethoxyphenyl)-6,8-dimethylquinoline-3-carboxylate (2k):



Starting from ethyl 4-chloro-6,8-dimethylquinoline-3-carboxylate (200 mg, 0.76 mmol), the product **2k** was isolated as light yellow crystals (176 mg, 64 %); mp = 105 – 107 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, ^{3}J = 7.1 Hz, 3H, CH_2CH_3), 2.38 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.14 (q, ^{3}J = 7.1Hz, 2H, CH_2CH_3), 6.69 (dd, ^{4}J = 2.7 Hz, ^{5}J = 0.7 Hz, 1H, CH_{Ar}), 6.91 – 7.05 (m, 2H CH_{Ar}), 7.18 (s, 1H, CH_{Ar}), 7.46 (s, 1H, CH_{Ar}), 9.35 (s, 1H, CH_{Ar}).

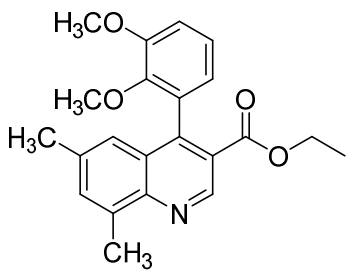
^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 18.4 (CH_3), 21.9 (CH_3), 55.9 (OCH_3), 56.4 (OCH_3), 61.0 (CH_2CH_3), 112.1 (CH), 114.1 (CH), 116.3 (CH), 123.3 (C), 124.1 (CH), 127.2 (C), 133.7 (CH), 136.8 (C), 136.8 (C), 146.4, 147.0 (C), 148.2 (CH), 151.1 (C), 153.5 (C), 166.6 (C=O). One Carbon signal cannot be detected.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052 (w), 2998 (w), 2986 (w), 2956 (w), 2936 (w), 2835 (w), 1724 (s), 1619 (w), 1566 (m), 1504 (s), 1493 (s), 1460 (s), 1441 (m), 1429 (m), 1408 (m), 1367 (m), 1356 (m), 1292 (s), 1262 (m), 1248 (m), 1232 (s), 1216 (s), 1194 (s), 1174 (s), 1141 (s), 1123 (s), 1095 (m), 1059 (s), 1033 (s), 1021 (s), 951 (m), 933 (m), 899 (m), 881 (m), 858 (s), 816 (s), 803 (m), 777 (m), 767 (m), 746 (s), 740 (s), 716 (s), 677 (m), 659 (m), 630 (m), 601 (m), 574 (m), 562 (m), 533 (m);

MS (GC, 70 eV) *m/z* (%): 366 (25), 365 ($[M]^+$, 100), 306 (22), 305 (17), 29 (52);

HRMS (EI): calcd. for $C_{22}H_{23}NO_4$ ($[M]^+$) 365.16216, found 365.16188.

Ethyl 4-(2,3-dimethoxyphenyl)-6,8-dimethylquinoline-3-carboxylate (2l):



Starting from ethyl 4-chloro-6,8-dimethylquinoline-3-carboxylate (200 mg, 0.76 mmol), the product **2l** was isolated as yellow crystals (222 mg, 80 %); mp = 120 – 122 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, ^3J = 7.1 Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.51 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.16 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.70 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, CH_{Ar}), 7.06 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.12 – 7.19 (m, 2H, CH_{Ar}), 7.46 (s, 1H, CH_{Ar}), 9.36 (s, 1H, CH_{Ar}).

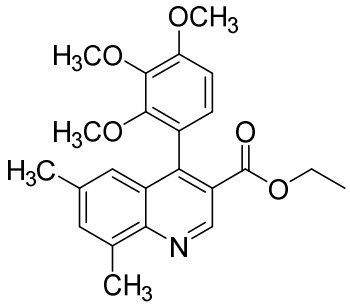
^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 18.4 (CH_3), 21.9 (CH_3), 55.9 (OCH_3), 60.6 (OCH_3), 61.1 (CH_2CH_3), 112.5 (CH), 122.0 (CH), 123.1 (C), 123.8 (CH), 124.3 (CH), 127.3 (C), 131.7 (C), 133.9 (CH), 136.8 (C), 136.9 (C), 146.3 (C), 146.8 (2*C, C), 148.2 (CH), 152.7 (C), 166.6 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2990 (w), 2968 (w), 2939 (w), 2828 (w), 1981 (w), 1906 (w), 1718 (s), 1618 (w), 1599 (w), 1569 (m), 1498 (w), 1471 (s), 1428 (m), 1391 (w), 1365 (m), 1293 (m), 1259 (s), 1248 (s), 1227 (m), 1199 (s), 1170 (s), 1145 (s), 1110 (s), 1081 (m), 1052 (s), 1024 (s), 995 (s), 956 (m), 887 (m), 856 (m), 816 (s), 784 (s), 761 (m), 750 (s), 710 (s), 650 (m), 623 (m), 603 (m), 561 (m);

MS (GC, 70 eV) *m/z* (%): 366 (22), 365 ($[M]^+$, 100), 334 (11), 320 (11), 307 (11), 306 (29), 292 (10), 262 (11), 234 (10), 29 (47);

HRMS (EI): calcd. for $C_{22}H_{23}NO_4$ ($[M]^+$) 365.16216, found 365.16189.

Ethyl 6,8-dimethyl-4-(2,3,4-trimethoxyphenyl)quinoline-3-carboxylate (2m):



Starting from ethyl 4-chloro-6,8-dimethylquinoline-3-carboxylate (200 mg, 0.76 mmol), the product **2m** was isolated as yellow crystals (225 mg, 75 %); mp = 98 – 100 ° C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 2.38 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.55 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.17 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.78 (s, 2H, CH_{Ar}), 7.19 (s, 1H, CH_{Ar}), 7.45 (s, 1H, CH_{Ar}), 9.32 (s, 1H, CH_{Ar}).

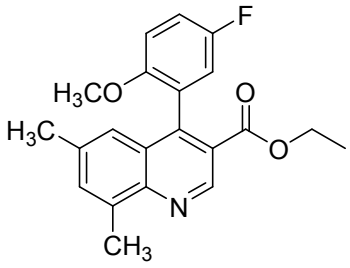
^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 18.7 (CH_3), 21.9 (CH_3), 56.2 (OCH_3), 60.9 (OCH_3), 61.05 (OCH_3), 61.1 (CH_2CH_3), 107.0 (CH), 123.6 (C), 123.7 (C), 124.2 (CH), 124.4 (CH), 127.6 (C), 133.7 (CH), 136.8 (C), 136.9 (C), 142.2, 146.3 (C), 146.90 (C), 148.2 (CH), 151.3 (C), 154.05 (C) , 166.8 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953 (w), 2838 (w), 1723 (m), 1596 (m), 1484 (m), 1459 (s), 1404 (m), 1367 (m), 1319 (m), 1288 (s), 1268 (s), 1250 (m), 1206 (s), 1170 (m), 1136 (m), 1085 (s), 1040 (s), 1004 (s), 956 (m), 945 (m), 923 (m), 910 (m), 891 (m), 860 (m), 814 (s), 705 (m), 685 (m), 671 (m), 623 (m), 545 (m);

MS (GC, 70 eV) *m/z* (%): 396 (27), 395 ($[M]^+$, 100), 364 (11), 336 (15), 214 (14), 29 (44);

HRMS (EI): calcd. for $C_{23}H_{25}NO_5$ ($[M]^+$) 395.17272, found 395.17262.

Ethyl 4-(5-fluoro-2-methoxyphenyl)-6,8-dimethylquinoline-3-carboxylate (2n):



Starting from ethyl 4-chloro-6,8-dimethylquinoline-3-carboxylate (200 mg, 0.76 mmol), the product **2n** was isolated as yellow crystals (188 mg, 70 %); mp = 97 – 98 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 2.39 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 4.17 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.86 (dd, ^3J = 8.4 Hz, ^4J = 3.1 Hz, 1H, CH_{Ar}), 6.96 (dd, ^3J = 9.0 Hz, ^4J = 4.3 Hz, 1H, CH_{Ar}), 7.12 (s, 1H, CH_{Ar}), 7.14 – 7.20 (m, 1H, CH_{Ar}), 7.47 (s, 1H, CH_{Ar}), 9.37 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 18.2 (CH_3), 21.8 (CH_3), 56.2 (OCH_3), 60.9 (CH_2CH_3), 111.70 (d, $^3J_{C\text{-}F}$ = 8.3 Hz, CH), 115.34 (d, $^2J_{C\text{-}F}$ = 22.6 Hz, CH), 117.14 (d, $^2J_{C\text{-}F}$ = 24.1 Hz, CH), 122.9 (C), 123.6 (CH), 126.80, 127.5 (d,

$^{3}J_{C\text{-}F}$ = 7.9 Hz, C), 133.7 (CH), 136.9 (C), 136.95 (C), 145.1 (d, $^{4}J_{C\text{-}F}$ = 0.8 Hz, C), 147.1 (C), 148.2 (CH), 152.9 (d, $^{4}J_{C\text{-}F}$ = 2.1 Hz, C), 156.7 (d, $^{1}J_{C\text{-}F}$ = 239.4 Hz, C), 166.2 (C=O).

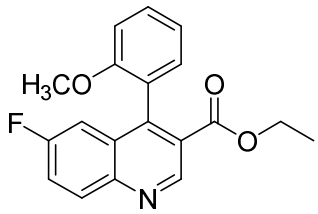
^{19}F NMR (282 MHz, $CDCl_3$): δ = -124.13 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3077 (w), 2983 (w), 2957 (w), 2940 (w), 2923 (w), 2839 (w), 1869 (w), 1723 (m), 1709 (m), 1620 (w), 1597 (w), 1569 (m), 1490 (s), 1456 (m), 1429 (m), 1365 (m), 1318 (s), 1294 (m), 1252 (s), 1232 (m), 1203 (m), 1179 (s), 1159 (s), 1143 (s), 1119 (s), 1057 (m), 1026 (s), 962 (m), 936 (m), 910 (m), 880 (m), 854 (s), 813 (s), 767 (m), 741 (s), 718 (s), 681 (m), 665 (m), 630 (m), 590 (m);

MS (GC, 70 eV) *m/z* (%): 354 (23), 353 ($[M]^+$, 100), 308 (12), 280 (17), 265 (16), 264 (14), 250 (22), 29 (47);

HRMS (EI): calcd. for $C_{21}H_{21}FNO_3$ ($[M]^+$) 353.14217, found 353.14233.

Ethyl 6-fluoro-4-(2-methoxyphenyl)quinoline-3-carboxylate (2o):



Starting from ethyl 4-chloro-6-fluoroquinoline-3-carboxylate (200 mg, 0.79 mmol), the product **2o** was isolated as white solid (228 mg, 89 %); mp = 231 – 233 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, ^{3}J = 7.1 Hz, 3H, CH_2CH_3), 3.68 (s, 3H, OCH_3), 4.14 (q, ^{3}J = 7.1 Hz, 2H, CH_2CH_3), 7.04 (d, ^{3}J = 8.3 Hz, 1H, CH_{Ar}), 7.09-7.11 (m, 2H, CH_{Ar}), 7.18 (dd, ^{3}J = 10 Hz, ^{3}J = 2.8 Hz, 1H, CH_{Ar}), 7.48-7.51 (m, 1H, CH_{Ar}), 7.51-7.54 (m, 1H, CH_{Ar}), 8.19 (dd, ^{3}J = 9.2 Hz, ^{3}J = 5.4 Hz, 1H, CH_{Ar}), 9.34 (s, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 55.7 (OCH_3), 61.3 (CH_2CH_3), 110.9 (d, $^{2}J_{C\text{-}F}$ = 23.3 Hz, CH), 110.9 (CH), 120.7 (CH), 121.1 (CH), 121.5 (CH), 124.4 (C), 125.1 (C), 128.5 (d, $^{2}J_{C\text{-}F}$ = 9.6 Hz, C), 130.2 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz, CH), 132.0 (d, $^{3}J_{C\text{-}F}$ = 9.1 Hz, CH), 146.4 (C), 146.9 (d, $^{4}J_{C\text{-}F}$ = 5.6 Hz, C), 149.6 (d, $^{4}J_{C\text{-}F}$ = 2.7 Hz, CH), 156.6 (C), 161.0 (d, $^{1}J_{C\text{-}F}$ = 248.5 Hz, C), 166.3 (C=O);

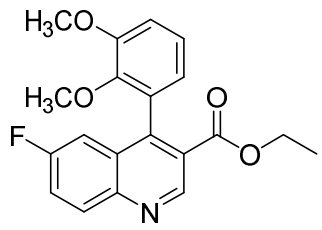
^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.64 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3056 (w), 2984 (w), 2961 (w), 2937 (w), 2901 (w), 2839 (w), 1702 (s), 1623 (m), 1574 (m), 1494 (s), 1461 (s), 1437 (m), 1423 (s), 1367 (m), 1317 (s), 1286 (m), 1256 (s), 1238 (s), 1220 (s), 1187 (s), 1109 (s), 1102 (s), 1047 (s), 1026 (s), 981 (s), 939 (s), 885 (s), 867 (m), 847 (s), 827 (m), 786 (s), 760 (s), 733 (s), 684 (m), 631 (m), 618 (s), 565 (s), 527 (s);

MS (EI, 70eV): *m/z* (%) = 326 ($[M+H]^+$, 19), 325 ($[M]^+$, 100), 294 (15), 280 (51), 279 (13), 267 (14), 266 (75), 265 (25), 252 (25), 251 (15), 250 (27), 238 (21), 237 (66), 232 (15), 222 (22), 221 (14), 209 (17), 208 (42), 205 (14), 204 (100), 183 (10), 182 (21), 181 (25), 29 (16);

HRMS (EI) calcd for $C_{19}H_{16}FNO_3$ ($[M]^+$) 325.11087, found 325.11088.

Ethyl 4-(2,3-dimethoxyphenyl)-6-fluoroquinoline-3-carboxylate (2p):



Starting from ethyl 4-chloro-6-fluoroquinoline-3-carboxylate (200 mg, 0.79 mmol), the product **2p** was isolated as yellow crystals (244 mg, 87 %); mp = 55 – 57 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 3.52 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.17 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.70 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, CH_{Ar}), 7.07 (dd, ^3J = 8.3 Hz, ^4J = 1.6 Hz, 1H, CH_{Ar}), 7.14-7.21 (m, 2H, CH_{Ar}), 7.53 (ddd, ^3J = 9.2 Hz, ^3J = 7.9 Hz, ^4J = 2.8 Hz, 1H, CH_{Ar}), 8.17 (dd, ^3J = 9.2 Hz, ^4J = 5.4 Hz, 1H, CH_{Ar}), 9.34 (s, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 56.0 (OCH_3), 60.7 (OCH_3), 61.4 (CH_2CH_3), 111.0 (d, $^2J_{C-F}$ = 23.3 Hz, CH), 113.0 (CH), 121.4 (d, $^2J_{C-F}$ = 25.9 Hz, CH), 121.8 (CH), 124.0 (C), 124.1 (CH), 128.4 (d, $^3J_{C-F}$ = 9.6 Hz, C), 130.7 (C), 132.1 (d, $^3J_{C-F}$ = 9.1 Hz, CH), 146.2, 146.4 (C), 146.6 (d, $^4J_{C-F}$ = 5.8 Hz, C), 149.7 (d, $^4J_{C-F}$ = 2.6 Hz, CH), 152.9 (C), 161.0 (d, $^1J_{C-F}$ = 248.8 Hz), 166.2 (C=O);

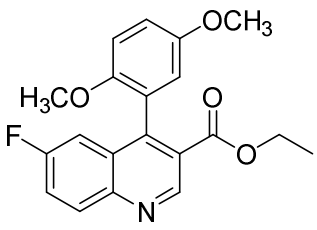
^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.14 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2990 (w), 2938 (w), 2829 (w), 1719 (s), 1569 (m), 1506 (s), 1468 (s), 1423 (s), 1362 (m), 1315 (s), 1259 (s), 1206, 1170 (s), 1111 (s), 1074 (s), 1001 (s), 837 (m), 731 (s);

MS (EI, 70eV): *m/z* (%) = 356 ($[M+H]^+$, 22), 355 (M^+, 100), 324 (13), 310 (18), 297 (12), 296 (10), 280 (15), 267 (10), 253 (23), 252 (25), 225 (12), 224 (22), 208 (12), 204 (30), 169 (13), 29 (16);

HRMS (EI) calcd for $C_{20}H_{18}FNO_4$ ($[M]^+$) 355.12144, found 355.12121.

Ethyl 4-(2,5-dimethoxyphenyl)-6-fluoroquinoline-3-carboxylate (2q):



Starting from ethyl 4-chloro-6-fluoroquinoline-3-carboxylate (200 mg, 0.79 mmol), the product **2q** was isolated as whitish crystals (241 mg, 86 %); mp = 96 – 98 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, ^{3}J = 7.1 Hz, 3H, CH_2CH_3), 3.62 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.16 (q, ^{3}J = 7.1 Hz, 2H, CH_2CH_3), 6.66 (d, ^{4}J = 2.4 Hz, 1H, CH_{Ar}), 6.98-7.03 (m, 2H, CH_{Ar}), 7.19 (dd, ^{3}J = 10.0 Hz, ^{4}J = 2.8 Hz, 1H, CH_{Ar}), 7.53 (ddd, ^{3}J = 9.2 Hz, ^{3}J = 7.9 Hz, ^{4}J = 2.8 Hz, 1H, CH_{Ar}), 8.17 (dd, ^{3}J = 9.2 Hz, ^{3}J = 5.4 Hz, 1H, CH_{Ar}), 9.33 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 56.0 (OCH_3), 56.3 (OCH_3), 61.3 (CH_2CH_3), 110.8 (d, $^{2}J_{C\text{-}F}$ = 23.2 Hz), 112.1, 114.6, 116.1, 121.3 (d, $^{2}J_{C\text{-}F}$ = 26.0 Hz), 124.3, 126.0, 128.3 (d, $^{3}J_{C\text{-}F}$ = 9.6 Hz), 132.2 (d, $^{3}J_{C\text{-}F}$ = 9.1 Hz), 146.4 (d, $^{4}J_{C\text{-}F}$ = 5.8 Hz), 146.5, 149.7 (d, $^{4}J_{C\text{-}F}$ = 2.7 Hz), 150.9, 153.6, 161.0 (d, $^{1}J_{C\text{-}F}$ = 248.5 Hz), 166.2 (C=O);

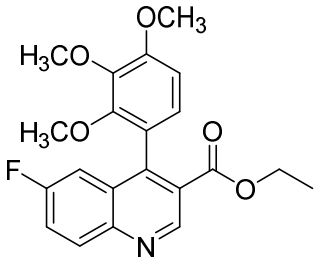
^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.64 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3034.2 (w), 2987 (w), 2933 (w), 2830 (w), 1734 (s), 1623 (w), 1575.5 (m), 1495 (s), 1462 (m), 1409 (m), 1364.5 (m), 1290 (m), 1225 (s), 1209 (s), 1193 (s), 1180 (s), 1111 (m), 1034 (s), 999 (m), 848 (s), 798 (s), 739.7 (s), 727 (m), 674.5 (m).

MS (EI, 70eV): *m/z* (%) = 356 ($[M+H]^+$, 22), 355 (M^+, 100), 296 (35), 280 (15), 268 (17), 253 (14), 252 (12), 225 (12), 224 (14), 169 (10), 29 (13).

HRMS (EI) calcd for $C_{20}H_{18}FNO_4$ ($[M]^+$) 355.12144, found 355.12155.

Ethyl 6-fluoro-4-(2,3,4-trimethoxyphenyl)quinoline-3-carboxylate (2r):



Starting from ethyl 4-chloro-6-fluoroquinoline-3-carboxylate (200 mg, 0.79 mmol), the product **2r** was isolated as light yellow crystals (264 mg, 87 %); mp = 111 – 113 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, ^{3}J = 7.1 Hz, 3H, CH_2CH_3), 3.58 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.18 (q, ^{3}J = 7.1 Hz, 2H, CH_2CH_3), 6.8 (s, 2H, CH_{Ar}), 7.22 (dd, ^{3}J = 10.0 Hz, ^{4}J = 2.7 Hz, 1H, CH_{Ar}), 7.53 (ddd, ^{3}J = 9.2 Hz, ^{3}J = 7.9 Hz, ^{4}J = 2.8 Hz, 1H, CH_{Ar}), 8.17 (dd, ^{3}J = 9.2 Hz, ^{3}J = 5.4 Hz, 1H, CH_{Ar}), 9.30 (s, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 56.3 (OCH_3), 61.0 (OCH_3), 61.1 (OCH_3), 61.44 (CH_2CH_3), 107.3 (CH), 110.9 (d, $^{2}J_{C\text{-}F}$ = 23.3 Hz, CH), 121.4 (d, $^{2}J_{C\text{-}F}$ = 26.1 Hz, CH), 122.7 (C), 124.3 (CH), 124.6, 128.8 (d, $^{3}J_{C\text{-}F}$ = 9.5 Hz, C), 132.0 (d, $^{3}J_{C\text{-}F}$ = 9.0 Hz, CH), 142.4 (C), 146.15 (C), 146.5 (C), 149.5 (d, $^{4}J_{C\text{-}F}$ = 2.5 Hz, CH), 151.2 (C), 154.6 (C), 161.1 (d, $^{1}J_{C\text{-}F}$ = 248.8 Hz), 166.3 (C=O);

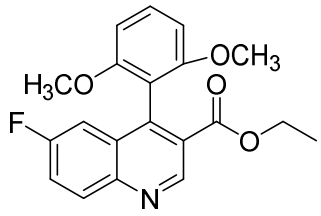
^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.3 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3066 (w), 2993 (w), 2972 (w), 2947 (w), 2845 (w), 1780 (s), 1602 (w), 1491 (m), 1463.5 (m), 1411 (m), 1321 (m), 1296 (m), 1181 (s), 1116 (m), 1092 (s), 1053 (s), 992.4 (m), 838 (m), 730.5 (m).

MS (EI, 70eV): *m/z* (%) = 386 ($[M+H]^+$, 19), 385 (M^+, 100), 326 (21), 310 (23), 282 (25), 254 (11), 239 (14), 204 (15), 183 (12), 29 (16).

HRMS (EI) calcd for $C_{21}H_{20}FNO_5$ ($[M]^+$) 385.13200, found 385.13172.

Ethyl 4-(2,6-dimethoxyphenyl)-6-fluoroquinoline-3-carboxylate (2s):



Starting from ethyl 4-chloro-6-fluoroquinoline-3-carboxylate (200 mg, 0.79 mmol), the product **2s** was isolated as yellow crystals (153 mg, 54.5 %); mp = 125 – 126 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 3.6 (s, 6H, 2*OCH_3), 4.15 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.70 (d, ^3J = 8.4 Hz, 2H, CH_{Ar}), 7.12 (dd, ^3J = 10.0 Hz, ^4J = 2.8 Hz, 1H, CH_{Ar}), 7.43 (t, ^3J = 8.4 Hz, 1H, CH_{Ar}), 7.51 (ddd, ^3J = 9.2 Hz, ^3J = 8.0 Hz, ^4J = 2.8 Hz, 1H, CH_{Ar}), 8.15 (dd, ^3J = 9.2 Hz, ^3J = 5.4 Hz, 1H, CH_{Ar}), 9.37 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 55.9 (s, 2*OCH_3), 61.1 (CH_2CH_3), 104.1 (CH), 110.6 (d, $^2J_{C-F}$ = 23.1 Hz, CH), 113.6 (C), 121.1 (d, $^2J_{C-F}$ = 26.0 Hz, CH), 124.8 (C), 128.7 (d, $^3J_{C-F}$ = 9.8 Hz), 130.5 (CH), 132.0 (d, $^3J_{C-F}$ = 9.2 Hz, CH), 144.3 (d, $^4J_{C-F}$ = 5.6 Hz, C), 146.4 (C), 149.9 (d, $^4J_{C-F}$ = 2.6 Hz, CH), 157.4 (C), 160.9 (d, $^1J_{C-F}$ = 247.6 Hz, C), 166.0 (C=O);

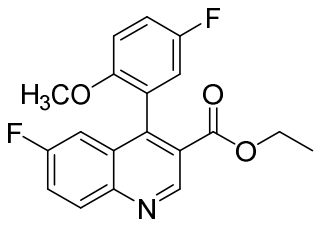
^{19}F NMR (282 MHz, $CDCl_3$): δ = -112.74 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (w), 2926 (w), 2850 (w), 2840 (w), 1702 (s), 1625 (w), 1582 (s), 1505 (m), 1485 (w), 1471 (s), 1459 (s), 1423 (s), 1390 (s), 1368 (m), 1357 (m), 1321 (s), 1300 (m), 1248 (s), 1217 (m), 1178 (s), 1104 (s), 1032 (s), 1017 (s), 980 (s), 957 (m), 944 (m), 904 (w), 863 (s), 835 (s), 792 (m), 781 (s), 763 (s), 743 (s), 726 (s), 632 (m), 620 (m), 607 (m), 596 (s), 574 (m), 566 (m), 544 (m);

MS (EI, 70eV): *m/z* (%) = 356 ($[M+H]^+$, 22), 355 (M^+, 100), 296 (35), 280 (15), 268 (17), 253 (14), 252 (12), 225 (12), 224 (14), 169 (10), 29 (13);

HRMS (EI) calcd for $C_{20}H_{18}FNO_4$ ($[M]^+$) 355.12199, found 355.12185.

Ethyl 6-fluoro-4-(5-fluoro-2-methoxyphenyl)quinoline-3-carboxylate (2t):



Starting from ethyl 4-chloro-6-fluoroquinoline-3-carboxylate (200 mg, 0.79 mmol), the product **2t** was isolated as yellow crystals (244mg, 90 %); mp = 92 – 94 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 3.64 (s, 3H, OCH_3), 4.17 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.87 (dd, ^3J = 8.2 Hz, ^4J = 3.1 Hz, 1H, CH_{Ar}), 6.97 (dd, ^3J = 9.2 Hz, ^4J = 4.3 Hz, 1H, CH_{Ar}), 7.12-7.21 (m, 2H, CH_{Ar}), 7.54 (ddd, ^3J = 9.2 Hz, ^3J = 7.9 Hz, ^4J = 3.1 Hz, 1H, CH_{Ar}), 8.18 (dd, ^3J = 9.2 Hz, ^3J = 5.4 Hz, 1H, CH_{Ar}), 9.36 (s, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 56.2 (OCH_3), 61.4 (CH_2CH_3), 110.5 (d, $^2J_{C\text{-}F}$ = 23.4 Hz, CH), 111.9 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, CH), 116.1 (d, $^2J_{C\text{-}F}$ = 22.7 Hz, CH), 117.1 (d, $^2J_{C\text{-}F}$ = 24.3 Hz, CH), 121.3 (d, $^2J_{C\text{-}F}$ = 26.0 Hz, CH), 124.1 (C), 126.4 (d, $^3J_{C\text{-}F}$ = 7.9 Hz), 128.05 (d, $^3J_{C\text{-}F}$ = 9.7 Hz, C), 132.2 (d, $^3J_{C\text{-}F}$ = 9.1 Hz, CH), 145.4 (d, $^4J_{C\text{-}F}$ = 4.4 Hz, C), 146.4 (C), 149.7 (d, $^4J_{C\text{-}F}$ = 2.7 Hz, CH), 152.85 (d, $^4J_{C\text{-}F}$ = 2.2 Hz, C), 156.9 (d, $^1J_{C\text{-}F}$ = 240.1 Hz, C), 161.1 (d, $^1J_{C\text{-}F}$ = 249.1 Hz, C), 165.8 (C=O).

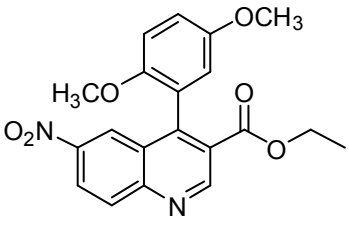
^{19}F NMR (282 MHz, $CDCl_3$): δ = -123.70 (CF), -111.12 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3140 (w), 3050 (w), 2919 (w), 2849 (w), 1921 (w), 1747 (s), 1620 (m), 1597 (w), 1562 (s), 1510 (s), 1483 (s), 1446 (m), 1421 (s), 1352 (m), 1330 (m), 1310 (m), 1287 (m), 1261 (m), 1232 (m), 1203 (s), 1163 (s), 1151 (s), 1116 (m), 1083 (s), 1004 (s), 986 (s), 965 (m), 890 (m), 858 (s), 837 (s), 821 (s), 753 (m), 742 (s), 727 (m), 709 (s), 682 (m), 661 (m), 648 (m), 605 (m), 595 (s), 546 (m);

MS (EI, 70eV): *m/z* (%) = 344 (20), 343 (100), 312 (13), 285 (14), 284 (87), 283 (25), 270 (13);

HRMS (EI) calcd for $C_{19}H_{15}F_2NO_3$ ($[M]^+$) 343.10145, found 343.10136.

Ethyl 4-(2,5-dimethoxyphenyl)-6-nitroquinoline-3-carboxylate (2u):



Starting from ethyl 4-chloro-6-nitroquinoline-3-carboxylate (200 mg, 0.71 mmol), the product **2u** was isolated as yellow crystals (140 mg, 51 %); mp = 164 – 166 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 3.64 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.20 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.70 (d, ^4J = 2.8 Hz, 1H, CH_{Ar}), 7.01 (d, ^3J = 9.0 Hz, 1H, CH_{Ar}), 7.08 (dd, ^3J = 9.0 Hz, ^4J = 2.8 Hz, 1H, CH_{Ar}), 8.31 (dd, ^3J = 9.0 Hz, ^5J = 0.5 Hz, 1H, CH_{Ar}), 8.50 (d, ^4J = 2.5 Hz, 1H, CH_{Ar}), 8.52 – 8.56 (m, 1H, CH_{Ar}), 9.5 (s, 1H, CH_{Ar}).

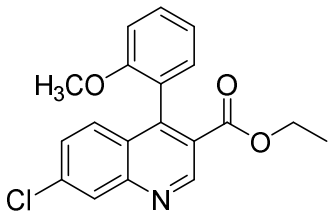
^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 56.0 (OCH_3), 56.2 (OCH_3), 61.7 (CH_2CH_3), 112.3 (CH), 115.4 (CH), 116.3 (CH), 124.4 (CH), 124.6 (CH), 124.6 (C), 125.6 (C), 126.6 (C), 131.5 (CH), 146.3 (C), 149.0 (C), 150.7 (C), 151.1 (C), 153.6 (CH), 153.8 (C), 165.6 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3091 (w), 3061 (w), 2993 (w), 2959 (w), 2937 (w), 2921 (w), 2838 (w), 1920 (w), 1850 (w), 1808 (w), 1723 (s), 1621 (m), 1573 (m), 1538 (m), 1504 (s), 1489 (s), 1465 (m), 1454 (m), 1440 (m), 1419 (m), 1411 (m), 1375 (w), 1338 (s), 1296 (m), 1282 (m), 1270 (m), 1210 (s), 1177 (s), 1141 (s), 1121 (m), 1076 (s), 1032 (s), 1003 (m), 965 (m), 904 (m), 886 (m), 844 (s), 807 (s), 746 (s), 729 (m), 694 (m), 669 (m), 640 (m), 619 (m), 592 (m), 563 (m), 551 (m), 529 (w);

MS (EI, 70eV): *m/z* (%) = 383 ($[M+H]^+$, 22), 382 ($[M]^+$, 100), 323 (20), 249 (20), 177 (11), 123 (11), 29 (14);

HRMS (EI): calcd. for $C_{20}H_{18}N_2O_6$ ($[M]^+$) 382.11594, found 382.11575.

Ethyl 7-chloro-4-(2-methoxyphenyl)quinoline-3-carboxylate (2v):



Starting from ethyl 4,7-dichloroquinoline-3-carboxylate (200 mg, 0.74 mmol), the product **2v** was isolated as yellow crystals (154 mg, 61.5 %); mp = 88 – 89 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, ^3J = 7.1 Hz, 1H, CH_2CH_3), 3.67 (s, 1H, OCH_3), 4.13 (q, ^3J = 7.1 Hz, 1H, CH_2CH_3), 7.03 (d, ^3J = 8.3 Hz, 1H, CH_{Ar}), 7.07-7.12 (m,2H, CH_{Ar}), 7.41 (dd, ^3J = 9.0 Hz, ^4J = 2.1 Hz, 1H, CH_{Ar}), 7.44 – 7.53 (m, 2H, CH_{Ar}), 8.17 (d, ^4J = 2.1 Hz, 1H, CH_{Ar}), 9.38 (s, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_2CH_3), 55.5 (OCH_3), 61.1 (CH_2CH_3), 110.8 (CH), 120.5 (CH), 123.75 (C), 125.0 (C), 125.7 (C), 128.1 (CH), 128.45 (CH), 128.9 (CH), 130.0 (CH), 130.1 (CH), 137.1 (C), 147.3 (C), 149.6 (C), 151.4 (CH), 156.5 (C), 166.1 (C=O).

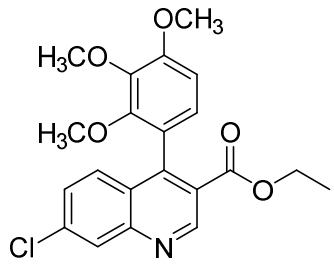
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3069 (w), 3000 (w), 2976 (w), 2933 (w), 2835 (w), 1709 (s), 1600 (m), 1583 (m), 1561 (m), 1497 (m), 1480 (m), 1461 (m), 1453 (m), 1435 (m), 1400 (m), 1368 (m), 1346 (w), 1318 (s), 1290 (m), 1253 (s), 1238 (s), 1207 (s), 1185 (m), 1163 (m), 1149 (s), 1122 (s), 1108 (s), 1070 (m), 1052 (m), 1027 (s), 988 (m), 964 (m), 956 (m), 923 (m), 881 (m), 828 (m), 790 (s), 764 (s), 712 (m), 674 (m), 624 (s), 582 (m), 571 (m), 545 (w), 533 (w);

MS (EI, 70eV): *m/z* (%) = 343 (35), 342 ([M+H]$^+$, 22), 341 ([M]$^+$, 100), 312 (13), 310 (25), 298 (23), 297 (17), 296 (68), 295 (12), 284 (26), 283 (19), 282 (83), 281 (15), 269 (10), 268 (29), 267 (13), 266 (28), 255 (21), 254 (20), 253 (59), 248 (16), 233 (12), 232 (15), 224 (11), 222 (29), 221 (13), 220 (91), 218 (20), 204 (15), 203 (11), 202 (12), 201 (14), 190 (39), 189 (13), 188 (12), 176 (16), 164 (14), 163 (31), 162 (11), 29 (49);

HRMS (EI) calcd for $C_{19}H_{16}{}^{35}ClNO_3$ ([M]$^+$) 341.08132, found 341.08159;

HRMS (EI) calcd for $C_{19}H_{16}{}^{37}ClNO_3$ ([M]$^+$) 343.07837, found 343.07916.

Ethyl 7-chloro-4-(2,3,4-trimethoxyphenyl)quinoline-3-carboxylate (2w):



Starting from ethyl 4,7-dichloroquinoline-3-carboxylate (200 mg, 0.74 mmol), the product **2w** was isolated as yellow crystals (196 mg, 72 %); mp = 104 – 105 °C;

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.11 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 3.56 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.19 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.78 (s, 2H, CH_{Ar}), 7.43 (dd, ^3J = 9.0 Hz, ^4J = 2.1 Hz, 1H, CH_{Ar}), 7.56 (d, ^3J = 9.0 Hz, 1H, CH_{Ar}), 8.16 (d, ^4J = 2.1 Hz, 1H, CH_{Ar}), 9.35 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 56.2 (OCH_3), 61.0 (OCH_3), 61.1 (OCH_3), 61.4 (CH_2CH_3), 107.2 (CH), 122.8 (C), 124.1 (C), 124.3 (CH), 126.1 (C), 128.3 (CH), 128.7 (CH), 129.0 (CH), 137.2 (C), 142.3 (C), 146.9 (C), 149.7 (C), 151.2 (C), 151.5 (CH), 154.5 (C), 166.3 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3062 (w), 2975 (w), 2936 (w), 2906 (w), 2836 (w), 1699 (s), 1598 (m), 1568 (m), 1498 (m), 1479 (m), 1462 (m), 1441 (m), 1411 (m), 1375 (m), 1366 (m), 1346 (w), 1318 (m), 1291 (s), 1261 (s), 1222 (s), 1206 (s), 1183 (m), 1166 (m), 1150 (m), 1125 (m), 1094 (s), 1073 (s), 1054 (s), 1013 (s), 995 (s), 947 (m), 934 (m), 917 (m), 894 (m), 877 (m), 864 (m), 846 (m), 829 (m), 815 (m), 794 (s), 759 (m), 691 (m), 684 (m), 658 (m), 635 (m), 610 (m), 599 (m), 565 (w), 530 (m);

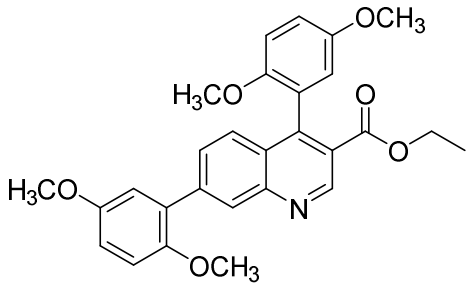
MS (EI, 70eV): *m/z* (%) = 402 ([M+H]$^+$, 22), 401 ([M]$^+$, 100), 342 (27), 326 (25), 300 (10), 298 (26), 255 (12), 220 (18), 164 (13), 153 (14), 29 (33);

HRMS (EI) calcd for $C_{21}H_{20}{}^{35}ClNO_5$ ([M]$^+$) 401.10245, found 401.10205;

HRMS (EI) calcd for $C_{21}H_{20}{}^{37}ClNO_5$ ([M]$^+$) 403.09950, found 403.09969.

Ethyl 4,7-bis(2,5-dimethoxyphenyl)quinoline-3-carboxylate (2x):

Starting from ethyl 4,7-dichloroquinoline-3-carboxylate (200 mg, 0.74 mmol), the product **2x** was isolated as yellow crystals (260mg, 65 %); mp = 231 – 233 °C;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, ^{3}J = 7.1 Hz, 3H, CH_2CH_3), 3.6 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.8 (s, 3H, OCH_3), 4.2 (q, ^{3}J = 7.1 Hz, 2H, CH_2CH_3), 6.7 (dd, ^{4}J = 2.7 Hz, ^{5}J = 0.5 Hz, 1H, CH_{Ar}), 6.92 (dd, ^{3}J = 8.9 Hz, ^{4}J = 2.9 Hz, 1H, CH_{Ar}), 6.95 (s, 1H, CH_{Ar}), 6.98 (s, 1H, CH_{Ar}), 6.99 (d, ^{4}J = 2.7 Hz, 1H, CH_{Ar}), 7.04 (t, ^{4}J = 2.7 Hz, 1H, CH_{Ar}), 7.62 (d, ^{3}J = 8.8 Hz, 1H, CH_{Ar}), 7.72 (dd, ^{3}J = 8.8 Hz, ^{4}J = 1.8 Hz, 1H, CH_{Ar}), 8.33 (d, ^{4}J = 1.5 Hz, 1H, CH_{Ar}), 9.40 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 56.0 (OCH_3), 56.05 (OCH_3), 56.4 (OCH_3), 56.4 (OCH_3), 61.1 (CH_2CH_3), 112.1 (CH), 112.9 (CH), 114.4 (CH), 114.5 (CH), 116.2 (CH), 116.7 (CH), 123.3 (C), 126.2 (C), 126.7 (C), 126.9 (CH), 129.4 (CH), 129.6 (CH), 130.3 (C), 141.6, 146.9, 149.5 (C), 150.6 (CH), 151.0 (C), 151.1 (C), 153.5 (C), 154.0 (C), 166.3 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3067 (w), 3001 (w), 2929 (w), 2832 (w), 1728 (s), 1613 (w), 1573 (m), 1495 (s), 1462 (s), 1454 (m), 1425 (m), 1417 (m), 1394 (w), 1378 (m), 1365 (m), 1348 (m), 1302 (m), 1286 (m), 1273 (m), 1286 (m), 1273 (m), 1225 (s), 1213 (s), 1179 (s), 1164 (s), 1154 (s), 1142 (s), 1134 (s), 1105 (m), 1041 (s), 1033 (s), 1019 (s), 942 (m), 927 (m), 886 (m), 871 (m), 838 (m), 820 (s), 795 (s), 763 (m), 743 (s), 733 (s), 728 (s), 697 (s), 682 (m), 664 (m), 637 (m), 621 (m), 601 (m), 581 (w), 547 (m), 536 (m);

MS (EI, 70eV): *m/z* (%) = 474 ($[M+H]^+$, 22), 473 ($[M]^+$, 100), 342 (27), 326 (25), 300 (10), 298 (26), 255 (12), 220 (18), 164 (13), 153 (14);

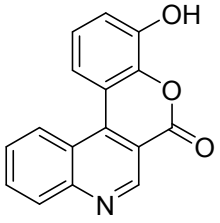
HRMS (EI) calcd for $C_{28}H_{27}NO_6$ ($[M]^+$) 473.18384, found 473.18389.

General procedure for the synthesis of compounds 3a-x:

To a solution of **2** in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added solution of boron tribromide (3 mmol). The cold bath was removed and the reaction mixture was allowed to warm to 23 °C. Upon removal of the cold bath, all of the boron tribromide went into solution to form a deep red homogenous solution, and as the temperature approaches 23 °C, a solid began to precipitate from solution. The mixture was stirred at

23 °C for 12 h and then quenched by the addition of MeOH (4 mL). Upon addition of MeOH solid redissolved and formed a red homogenous solution. After stirring for 15 min organic solvents were concentrated under reduced pressure. Upon addition of water (10 mL), a bright yellow precipitate was formed and collected by filtration and additionaly washed with water (5mL) to provide pure 6*H*-chromeno[3,4-*c*]quinolin-6-ones **3**.

4-hydroxy-6*H*-chromeno[3,4-*c*]quinolin-6-one (3a):



Starting from compound **2a** (100 mg, 0.29 mmol), the product **3a** was isolated as yellow solid (69 mg, 88 %); mp = 278 – 280 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.27 (dd, ^3J = 8.0 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.36 (t, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.88 (ddd, ^3J = 8.4 Hz, ^3J = 7.0 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 8.04 (ddd, ^3J = 8.3 Hz, ^3J = 6.9 Hz, ^4J = 1.2 Hz, 1H, CH_{Ar}), 8.13 (dd, ^3J = 8.2 Hz, ^4J = 0.9 Hz, 1H, CH_{Ar}), 8.24 (dd, ^3J = 8.4 Hz, ^4J = 0.9 Hz, 1H, CH_{Ar}), 8.95 (d, ^3J = 8.5 Hz, 1H, CH_{Ar}), 9.50 (s, 1H, CH_{Ar}), 10.39 (s, 1H, OH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 113.8 (C), 117.5 (C), 118.7 (CH), 119.0 (CH), 121.7 (C), 124.8 (CH), 127.2 (CH), 128.65 (CH), 129.9 (CH), 132.4 (CH), 140.9 (CH), 141.5 (C), 145.8 (C), 149.05 (C), 149.7 (C), 159.5 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079 (w), 3052 (w), 2918 (w), 2834 (w), 2724 (w), 2128 (w), 1884 (w), 1733 (m), 1621 (m), 1593 (m), 1578 (m), 1558 (s), 1514 (s), 1485 (s), 1426 (m), 1374 (m), 1359 (s), 1320 (m), 1304 (s), 1265 (m), 1251 (m), 1236 (m), 1205 (s), 1175 (m), 1157 (m), 1119 (m), 1104 (s), 1017 (s), 985 (m), 942 (m), 890 (w), 859 (m), 843 (s), 824 (s), 814 (m), 790 (m), 757 (s), 745 (s), 713 (m), 688 (m), 667 (m), 651 (m), 610 (m), 602 (s), 551 (w), 530 (m);

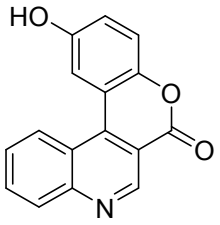
MS (EI, 70eV): *m/z* (%) = 264 ([M+H]$^+$, 19), 263 ([M]$^+$, 100), 235 (44), 207 (11), 179 (13), 178 (18), 152 (15), 151 (17), 76 (12);

HRMS (EI) calcd for $C_{16}H_9NO_3$ ([M]$^+$) 263.05769, found 263.05793.

2-hydroxy-6*H*-chromeno[3,4-*c*]quinolin-6-one (3b):

Starting from compound **2a** (100 mg, 0.29 mmol), the product **3a** was isolated as yellow solid (69 mg, 88 %); mp = 278 – 280 °C;

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.17 (dd, ^3J = 8.9 Hz, ^4J = 2.6 Hz, 1H, CH_{Ar}), 7.43 (d, ^3J = 8.9 Hz, 1H, CH_{Ar}), 7.88 (t, ^3J = 7.5 Hz, 1H, CH_{Ar}), 8.01 – 8.06 (m,



2H, CH_{Ar}), 8.22 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 8.87 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 9.4 (s, 1H, CH_{Ar}), 9.9 (s, 1H, OH).

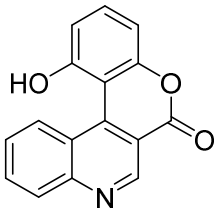
^{13}C NMR (63 MHz, DMSO-d_6): δ = 113.2, 113.8, 117.0, 118.8, 120.4, 121.5, 126.6, 128.5, 130.4, 132.2, 139.9, 145.7, 149.3, 150.1, 154.2, 159.8;

IR (ATR, cm-1): $\tilde{\nu}$ = 3500 (w), 3307 (w), 2918 (br. m), 2849 (br. m), 2668 (br. m), 1731 (s), 1557 (m), 1434 (m), 1352 (m), 1251 (m), 1230 (m), 113 (m), 1105 (m), 769 (s), 751 (s), 657 (m), 594 (s), 546 (m);

MS (GC-MS): m/z (%) = 264 ([M+H]$^+$, 17), 263 ([M]$^+$, 100), 235 (30), 207 (17), 97 (11), 83 (11), 73 (12), 69 (26), 60 (16), 57 (15), 55 (18), 44 (71), 43 (42), 41 (13).

HRMS (ESI): calcd. for $C_{16}H_9NO_3$ ([M+H]$^+$) 263.05769, found 263.05765.

1-hydroxy-6*H*-chromeno[3,4-*c*]quinolin-6-one (3c):



Starting from compound **2c** (100 mg, 0.29 mmol), the product **3c** was isolated as yellow solid (34 mg, 43 %); mp = 269 – 270 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.00 (d, ^3J = 8.2 Hz, 2H, CH_{Ar}), 7.56 (t, ^3J = 8.2 Hz, 1H, CH_{Ar}), 7.67 (t, ^3J = 7.3 Hz, 1H, CH_{Ar}), 7.94 (t, ^3J = 7.3 Hz, 1H, CH_{Ar}), 8.12 (d, ^3J = 8.3 Hz, 1H, CH_{Ar}), 8.39 (d, ^3J = 8.3 Hz, 1H, CH_{Ar}), 9.42 (s, 1H, CH_{Ar}), 11.12 (s, 1H, OH).

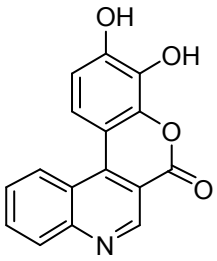
^{13}C NMR (63 MHz, DMSO-d_6): δ = 105.6 (C), 107.4 (CH), 112.55 (CH), 114.4 (C), 121.4 (C), 125.3 (CH), 128.55 (CH), 130.4 (CH), 132.1 (CH), 133.1 (CH), 141.3 (C), 148.2 (CH), 149.9 (C), 153.5 (C), 156.0 (C), 159.8 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3043 (w), 2921 (w), 2850 (w), 2600 (w), 1749 (s), 1607 (s), 1593 (m), 1576 (m), 1553 (m), 1507 (m), 1455 (m), 1418 (m), 1356 (s), 1301 (s), 1280 (s), 1218 (m), 1196 (m), 1154 (m), 1125 (m), 1089 (m), 1047 (s), 1017 (m), 975 (m), 911 (m), 870 (w), 835 (m), 798 (m), 759 (s), 731 (s), 670 (m), 642 (m), 627 (m), 592 (m), 560 (s), 528 (m);

MS (EI, 70eV): *m/z* (%) = 264 ([M+H]$^+$, 17), 263 ([M]$^+$, 100), 262 (62), 235 (40), 178 (22), 152 (11), 151 (15), 76 (11);

HRMS (ESI): calcd. for $C_{16}H_9NO_3$ ([M+H]$^+$) 263.05769, found 263.05775;

3,4-dihydroxy-6*H*-chromeno[3,4-*c*]quinolin-6-one (3d):



Starting from compound **2d** (100 mg, 0.27 mmol), the product **3d** was isolated as yellow solid (69 mg, 90 %); mp = 300 – 302 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.00 (d, ^{3}J = 8.8 Hz, 1H, CH_{Ar}), 7.82 (d, ^{3}J = 7.2 Hz, 1H, CH_{Ar}), 7.94 – 8.10 (m, 2H, CH_{Ar}), 8.16 (d, ^{3}J = 8.4 Hz, 1H, CH_{Ar}), 8.87 (d, ^{3}J = 8.0 Hz, 1H, CH_{Ar}), 9.41 (d, ^{3}J = 8.7 Hz, 1H, CH_{Ar}), 9.53 (s, 1H, OH), 10.47 (s, 1H, OH).

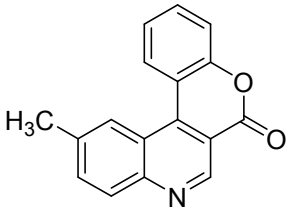
^{13}C NMR (63 MHz, DMSO-d_6): δ = 109.3, 111.7 (C), 112.8 (CH), 119.7 (CH), 121.6 (C), 127.3 (CH), 128.2 (CH), 130.0 (CH), 132.1 (CH), 133.2 (C), 141.5 (C), 143.0 (C), 149.3 (CH), 149.9 (C), 150.2 (C), 160.0 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3036 (w), 2919 (w), 2849 (w), 2724 (w), 1715 (m), 1600 (m), 1573 (s), 1557 (s), 1503 (s), 1449 (s), 1366 (m), 1350 (m), 1292 (s), 1266 (s), 1186 (s), 1128 (s), 1102 (s), 1076 (s), 1039 (s), 1020 (s), 960 (m), 931 (m), 890 (m), 869 (m), 788 (m), 765 (s), 748 (s), 718 (s), 659 (s), 605 (m), 577 (s), 527 (s);

MS (EI, 70eV): *m/z* (%) = 280 ([M+H]$^{+}$, 15), 279 (M^{+}, 100), 251 (21);

HRMS (ESI-TOF) calcd for $C_{16}H_9NO_4$ ([M-H]$^{+}$) 278.04588, found 278.04627.

11-methyl-6*H*-chromeno[3,4-*c*]quinolin-6-one (3e):



Starting from compound **2e** (100 mg, 0.31 mmol), the product **3e** was isolated as yellow solid (62 mg, 76 %); mp = 219 – 220°C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.57 (s, 1H, CH_3), 7.47 (dd, ^{3}J = 8.4 Hz, ^{4}J = 1.1 Hz, 1H, CH_{Ar}), 7.49 – 7.53 (m, 1H, CH_{Ar}), 7.71 (ddd, ^{3}J = 8.3 Hz, ^{3}J = 7.2 Hz, ^{4}J = 1.4 Hz, 1H, CH_{Ar}), 7.8 (dd, ^{3}J = 8.5 Hz, ^{4}J = 1.6 Hz, 1H, CH_{Ar}), 8.00 (d, ^{3}J = 8.5 Hz, 1H, CH_{Ar}), 8.49 (s, 1H, CH_{Ar}), 8.58 (d, ^{3}J = 8.2 Hz, 1H, CH_{Ar}), 9.28 (s, 1H, CH_{Ar}).

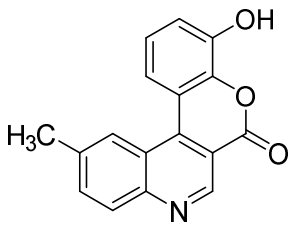
^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.5 (CH_3), 113.9 (C), 116.8 (C), 117.8 (CH), 121.50 (C), 125.1 (CH), 125.7 (CH), 128.9 (CH), 130.0 (CH), 132.5 (CH), 134.3 (CH), 138.8 (C), 139.4 (C), 148.2 (CH), 148.6 (C), 152.5 (C), 159.7 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3420 (w), 3060 (w), 2923 (w), 2852 (w), 1715 (s), 1606 (s), 1591 (s), 1567 (s), 1550 (s), 1510 (s), 1487 (m), 1454 (m), 1421 (s), 1377 (m), 1354 (s), 1309 (m), 1272 (m), 1241 (m), 1218 (s), 1159 (m), 1129 (m), 1118 (m), 1094 (s), 1045 (m), 982 (s), 961 (m), 946 (m), 896 (m), 870 (m), 828 (s), 797 (m), 764 (s), 751 (s), 725 (s), 678 (m), 661 (m), 650 (m), 626 (m), 605 (s), 590 (m), 530 (m);

MS (GC/MS, 70eV): *m/z* (%) = 262 ([M+H]$^{+}$, 19), 261 ([M]$^{+}$, 100), 246 (15), 234 (13), 233 (73), 232 (25), 218 (14), 204 (11), 190 (11), 176 (15), 88 (12);

HRMS (EI) calcd for $C_{17}H_{11}NO_2$ ([M]$^+$) 261.07843, found 261.07839.

4-hydroxy-11-methyl-6*H*-chromeno[3,4-*c*]quinolin-6-one (3f):



Starting from compound **2f** (100 mg, 0.285 mmol), the product **3f** was isolated as yellow solid (64 mg, 81 %); mp = 299 – 301 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.6 (s, 3H, CH_3), 7.23 (dd, ^3J = 8.0 Hz, ^4J = 1.2 Hz, 1H, CH_{Ar}), 7.31 (t, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.79 (dd, ^3J = 8.5 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 8.03 (dd, ^3J = 8.3 Hz, ^4J = 2.4 Hz, 2H, CH_{Ar}), 8.55 (s, 1H, CH_{Ar}), 9.34 (s, 1H, CH_{Ar}), 10.33 (s, 1H, OH).

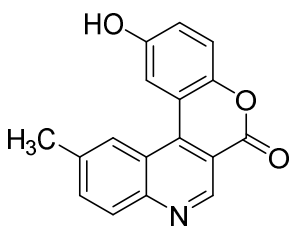
^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.45 (CH_3), 113.7 (C), 117.6 (C), 118.6 (CH), 118.7 (CH), 121.6 (C), 124.70 (CH), 125.8 (CH), 129.82 (CH), 134.1 (CH), 138.45 (C), 139.8 (C), 141.3 (C), 145.75 (C), 148.2 (CH), 148.5 (C), 159.55 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3072 (w), 3041 (w), 2917 (w), 2852 (w), 2744 (w), 1741 (m), 1719 (s), 1620 (w), 1574 (s), 1556 (m), 1512 (m), 1483 (m), 1425 (m), 1355 (s), 1324 (m), 1299 (s), 1280 (m), 1230 (m), 1217 (m), 1196 (m), 1157 (m), 1141 (s), 1096 (m), 1053 (m), 972 (m), 943 (m), 927 (m), 867 (m), 828 (s), 800 (m), 768 (s), 748 (s), 729 (s), 648 (m), 633 (m), 592 (m), 559 (s);

MS (GC, 70 eV) *m/z* (%): 278 (19), 277 ([M]$^+$, 100), 249 (48), 248 (18), 221 (10), 192 (10), 165 (13), 82 (12);

HRMS (EI): calcd. for $C_{17}H_{11}NO_3$ ([M]$^+$) 277.07334, found 277.07336.

2-hydroxy-11-methyl-6*H*-chromeno[3,4-*c*]quinolin-6-one (3g):



Starting from compound **2g** (100 mg, 0.285 mmol), the product **3g** was isolated as yellow solid (69 mg, 87 %); mp = 229–230 °C;

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.65 (s, 1H, CH_3), 7.2 (d, ^3J = 7.4 Hz, 1H, CH_{Ar}), 7.4 (d, ^3J = 8.4 Hz, 1H, CH_{Ar}), 7.9 (d, ^3J = 8.3 Hz, 1H, CH_{Ar}), 8.03 – 8.21 (m, 2H, CH_{Ar}), 8.65 (s, 1H, CH_{Ar}), 9.40 (s, 1H, CH_{Ar}), 9.96 (s, 1H, OH).

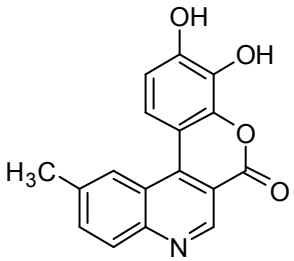
^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.6 (CH_3), 113.2 (CH), 113.8 (C), 117.2 (C), 118.8 (CH), 120.2 (CH), 121.6 (C), 125.45 (CH), 130.1 (CH), 134.1 (CH), 138.5 (C), 139.2 (C), 145.65 (C), 148.4 (CH), 148.7 (C), 154.10 (C), 159.9 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3014 (w), 2918 (w), 2814 (w), 2704 (w), 2624 (w), 1733 (m), 1621 (w), 1591 (m), 1573 (m), 1553 (s), 1512 (m), 1483 (s), 1420 (m), 1372 (m), 1356 (s), 1323 (m), 1303 (s), 1274 (m), 1236 (m), 1216 (m), 1205 (m), 1183 (s), 1132 (s), 1100 (m), 1027 (m), 1003 (m), 965 (m), 939 (m), 889 (w), 860 (m), 822 (s), 813 (s), 747 (s), 712 (m), 686 (m), 663 (m), 652 (m), 602 (m), 548 (w);

MS (EI, 70eV): *m/z* (%) = 278 ($[M+H]^+$, 15), 277 ($[M]^+$, 100), 249 (25);

HRMS (EI) calcd for $C_{17}H_{11}NO_3$ ($[M]^+$) 277.07334, found 277.07368.

3,4-dihydroxy-11-methyl-6*H*-chromeno[3,4-*c*]quinolin-6-one (3h):



Starting from compound **2h** (100 mg, 0.26 mmol), the product **3h** was isolated as yellow solid (69 mg, 90 %); mp = 350 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.62 (s, 3H, CH_3), 5.52 (br.s, 2H), 7.04 (d, ^3J = 9.0 Hz, 1H, CH_{Ar}), 7.93 (dd, ^3J = 8.6 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 8.08 (d, ^3J = 9.4 Hz, 1H, CH_{Ar}), 8.11 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 8.64 (s, 1H, CH_{Ar}), 9.47 (s, 1H, CH_{Ar}).

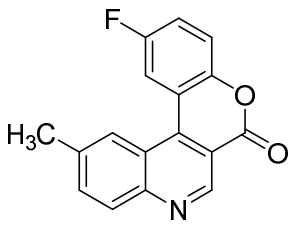
^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.4 (CH_3), 108.95 (C), 111.90 (C), 113.25 (CH), 120.85 (CH), 122.05 (C), 125.9 (CH), 126.75 (CH), 133.2 (C), 135.6 (CH), 139.6 (C), 143.1 (C), 143.3 (C), 144.1 (C), 146.5 (CH), 151.7 (C), 159.1 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3578 (w), 3396 (w), 3090 (m), 2975 (w), 2924 (w), 2885 (w), 2751 (m), 1945 (w), 1842 (w), 1730 (s), 1610 (m), 1597 (m), 1565 (s), 1493 (m), 1445 (s), 1401 (s), 1380 (s), 1353 (s), 1309 (m), 1289 (s), 1268 (s), 1250 (s), 1205 (s), 1149 (m), 1117 (m), 1083 (m), 1037 (m), 1013 (w), 976 (w), 954 (w), 872 (m), 827 (m), 815 (m), 795 (m), 779 (s), 742 (s), 709 (m), 688 (s), 669 (m), 605 (m), 590 (m), 572 (m);

MS (EI, 70eV): *m/z* (%) = 294 ($[M+H]^+$, 32), 293 ($[M]^+$, 100), 278 (10), 265 (39), 264 (11), 84 (20), 82 (27), 80 (26), 66 (22);

HRMS (ESI-TOF) calcd for $C_{17}H_{11}NO_4$ ($[M+H]^+$) 294.07608, found 294.07614.

2-fluoro-11-methyl-6*H*-chromeno[3,4-*c*]quinolin-6-one (3i):



Starting from compound **2i** (100 mg, 0.29 mmol), the product **3i** was isolated as yellow solid (45 mg, 55 %); mp = 225 – 226 °C;

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.67 (s, 3H, CH_3), 7.6 (dd, ^3J = 7.0 Hz, ^4J = 2.1 Hz, 2H, CH_{Ar}), 7.86 (dd, ^3J = 8.5 Hz,

^4J = 1.6 Hz, 1H, CH_{Ar}), 8.12 (d, ^3J = 8.5 Hz, 1H, CH_{Ar}), 8.37 – 8.50 (m, 1H, CH_{Ar}), 8.61 (s, 1H, CH_{Ar}), 9.42 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 20.8 (CH_3), 113.3 (C), 113.9 (d, $^2J_{C\text{-}F}$ = 26.3 Hz, CH), 117.4 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, C), 118.9 (d, $^2J_{C\text{-}F}$ = 24.3 Hz, CH), 119.1 (d, $^3J_{C\text{-}F}$ = 8.7 Hz, CH), 120.9 (C), 124.5 (CH), 129.6 (CH), 133.7 (CH), 137.8 (d, $^4J_{C\text{-}F}$ = 2.5 Hz, C), 138.5 (C), 147.6 (CH), 148.4 (d, $^4J_{C\text{-}F}$ = 2.0 Hz, C), 148.5 (C), 157.8 (d, $^1J_{C\text{-}F}$ = 241.6 Hz, C), 158.7 (C=O).

^{19}F NMR (235 MHz, DMSO-d_6): δ = -116.00 (CF).

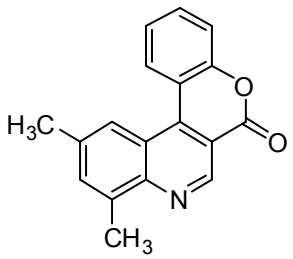
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3135 (w), 3088 (w), 3036 (w), 2952 (w), 2921 (w), 2851 (w), 1881 (w), 1740 (s), 1623 (w), 1598 (w), 1569 (s), 1555 (s), 1512 (m), 1485 (s), 1433 (s), 1417 (m), 1377 (m), 1350 (s), 1330 (m), 1307 (m), 1291 (m), 1264 (s), 1236 (m), 1221 (s), 1172 (s), 1134 (s), 1090 (s), 1014 (s), 999 (s), 963 (m), 941 (m), 894 (m), 869 (m), 851 (m), 834 (s), 818 (s), 752 (s), 741 (s), 728 (m), 709 (m), 684 (m), 657 (m), 649 (m), 597 (s), 541 (m);

MS (EI, 70eV): *m/z* (%) = 280 ($[M+H]^+$, 18), 279 ($[M]^+$, 100), 264 (14), 252 (14), 251 (77), 250 (29), 236 (18), 194 (11);

HRMS (EI) calcd for $C_{17}H_{10}FNO_2$ ($[M]^+$) 279.06901, found 279.06917.

9,11-dimethyl-6*H*-chromeno[3,4-*c*]quinolin-6-one (3j):

Starting from compound **2j** (100 mg, 0.298 mmol), the product **3j** was isolated as yellow solid (65 mg, 79 %); mp = 231 – 232 °C;



^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.59 (s, 1H, CH_3), 2.77 (s, 1H, CH_3), 7.45 – 7.60 (m, 2H, CH_{Ar}), 7.64 – 7.79 (m, 2H, CH_{Ar}), 8.42 – 8.51 (m, 1H, CH_{Ar}), 8.58 – 8.70 (m, 1H, CH_{Ar}), 9.40 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 17.6 (CH_3), 22.3 (CH_3), 113.0 (C), 116.6 (C), 117.2 (CH), 121.1 (C), 122.8 (CH), 124.3 (CH), 128.3 (CH), 131.7 (CH), 133.9 (CH), 133.9 (C), 136.9 (C), 137.5 (C), 146.3 (CH), 146.35 (C), 152.0 (C), 159.0 (C=O);

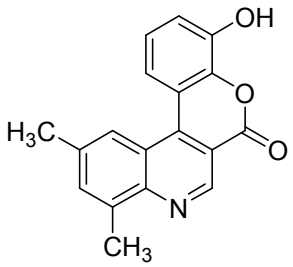
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3084 (w), 3005 (w), 2986 (w), 2947 (w), 2914 (w), 2603 (m), 1998 (w), 1873 (w), 1730 (s), 1620 (w), 1600 (m), 1567 (s), 1480 (m), 1446 (w), 1417 (m), 1405 (m), 1372 (m), 1349 (m), 1305 (m), 1269 (m), 1238 (m), 1205 (m), 1197 (s), 1158 (m), 1141 (m), 1105 (s), 1035 (m), 1002 (m), 928 (w), 881 (s), 811 (m),

798 (m), 761 (s), 730 (m), 676 (w), 655 (m), 629 (m), 609 (m), 584 (m), 554 (m), 528 (w);

MS (EI, 70eV): *m/z* (%) = 276 ($[M+H]^+$, 21), 275 (M^+, 100), 247 (15), 232 (18);

HRMS (ESI-TOF): calcd. for $C_{18}H_{13}NO_2$ ($[M+H]^+$) 275.09463, found 275.09471.

4-hydroxy-9,11-dimethyl-6*H*-chromeno[3,4-*c*]quinolin-6-one (3k):



Starting from compound **2k** (100 mg, 0.27 mmol), the product **3k** was isolated as yellow solid (65 mg, 82 %); mp = 249 – 251 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.5 (s, 3H+solvent, CH_3), 2.7 (s, 3H, CH_3), 7.22 (d, ^3J = 7.5 Hz, 1H, CH_{Ar}), 7.29 (t, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.64 (s, 1H, CH_{Ar}), 7.95 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 8.33 (s, 1H, CH_{Ar}), 9.32 (s, 1H, CH_{Ar}), 10.30 (s, 1H, OH).

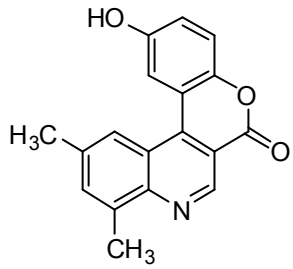
^{13}C NMR (63 MHz, DMSO-d_6): δ = 18.2 (CH_3), 21.5 (CH_3), 113.4 (C), 117.7 (C), 118.6 (CH), 118.8 (CH), 121.5 (C), 123.7 (CH), 124.6 (CH), 134.3 (CH), 137.3 (C), 137.75 (C), 139.8 (C), 141.2 (C), 145.8 (C), 147.05 (CH), 147.4 (C), 159.6 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3446 (w), 3040 (w), 2947 (w), 2847 (w), 2781 (w), 2734 (w), 2671 (w), 2642 (w), 1693 (s), 1613 (m), 1574 (s), 1557 (m), 1509 (m), 1479 (m), 1459 (m), 1411 (s), 1375 (s), 1351 (s), 1318 (m), 1299 (s), 1266 (m), 1251 (m), 1196 (m), 1184 (m), 1162 (s), 1100 (m), 1089 (m), 1016 (m), 987 (w), 960 (m), 934 (m), 879 (m), 844 (m), 810 (m), 790 (s), 775 (s), 756 (s), 724 (s), 701 (s), 601 (s), 558 (s);

MS (EI, 70eV): *m/z* (%) = 292 ($[M+H]^+$, 20), 291 ($[M]^+$, 100), 263 (12), 248 (12);

HRMS (EI): calcd. for $C_{18}H_{13}NO_3$ ($[M]^+$) 291.08899, found 291.08917.

2-hydroxy-9,11-dimethyl-6*H*-chromeno[3,4-*c*]quinolin-6-one (3l):



Starting from compound **2l** (100 mg, 0.27 mmol), the product **3l** was isolated as yellow solid (69 mg, 86 %); mp = 258 – 260°C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.50 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 7.09 (dd, ^3J = 8.9 Hz, ^4J = 2.5 Hz, 1H, CH_{Ar}), 7.33 (d, ^3J = 8.9 Hz, 1H, CH_{Ar}), 7.57 (s, 1H, CH_{Ar}), 7.86 (d, ^4J = 2.5 Hz, 1H, CH_{Ar}), 8.22 (s, 1H, CH_{Ar}), 9.21 (s, 1H, CH_{Ar}).

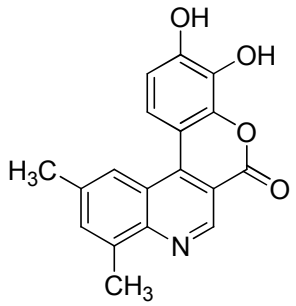
^{13}C NMR (63 MHz, DMSO-d_6): δ = 18.2 (CH_3), 21.6 (CH_3), 113.2 (CH), 113.3 (C), 116.9 (C), 118.6 (CH), 120.1 (CH), 121.3 (C), 123.15 (CH), 134.2 (CH), 137.1 (C), 137.7 (C), 139.1 (C), 145.4 (C), 146.8 (CH), 146.9 (C), 153.9 (C), 159.7 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3441 (w), 3066 (w), 3021 (w), 2947 (w), 2890 (w), 2801 (w), 2768 (w), 1985 (w), 1907 (w), 1861 (w), 1731 (s), 1622 (m), 1592 (m), 1573 (s), 1557 (s), 1499 (w), 1483 (m), 1454 (m), 1426 (s), 1411 (m), 1386 (m), 1352 (s), 1315 (m), 1302 (s), 1240 (s), 1202 (s), 1192 (s), 1157 (m), 1139 (s), 1108 (m), 1025 (m), 1011 (m), 982 (m), 958 (w), 851 (s), 835 (s), 808 (m), 792 (s), 756 (m), 745 (m), 723 (m), 669 (s), 604 (s), 560 (m);

MS (EI, 70eV): *m/z* (%) = 292 ([M+H]$^+$, 19), 291 ([M]$^+$, 100), 281 (13), 248 (12), 209 (11), 208 (19), 207 (75), 191 (13), 96 (11), 73 (12), 44 (35), 32 (16);

HRMS (EI): calcd. for $C_{18}H_{13}NO_3$ ([M]$^+$) 291.08899, found 291.08918.

3,4-dihydroxy-9,11-dimethyl-6H-chromeno[3,4-*c*]quinolin-6-one (3m):



Starting from compound **2m** (100 mg, 0.25 mmol), the product **3m** was isolated as yellow solid (51 mg, 65 %); mp = 318 – 320 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.49 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 6.95 (d, ^3J = 9.0 Hz, 1H, CH_{Ar}), 7.58 (s, 1H, CH_{Ar}), 7.88 (d, ^3J = 9.0 Hz, 1H, CH_{Ar}), 8.28 (s, 1H, CH_{Ar}), 9.23 (s, 1H, CH_{Ar}), 9.47 (broad s, 1H, OH), 10.38 (broad s, 1H, OH).

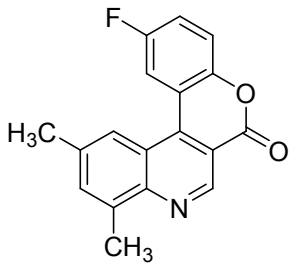
^{13}C NMR (63 MHz, DMSO-d_6): δ = 18.25 (CH_3), 21.4 (CH_3), 109.5, 111.3 (C), 112.6 (CH), 119.6 (CH), 121.4 (C), 123.8 (CH), 133.1 (C), 134.1 (CH), 137.1 (C), 137.2 (C), 140.6 (C), 142.66 (C), 147.1 (CH), 147.3 (C), 149.7(C), 160.05 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3477 (w), 3160 (w), 2919 (w), 2849 (w), 2850 (w), 1698 (s), 1614 (m), 1579 (m), 1557 (m), 1501 (m), 1458 (m), 1406 (m), 1372 (s), 1350 (s), 1313 (s), 1249 (m), 1209 (m), 1187 (m), 1158 (s), 1111 (s), 1048 (s), 1017 (m), 959 (m), 926 (m), 860 (m), 825 (m), 784 (s), 751 (m), 722 (m), 671 (m), 606 (m), 553 (s);

MS (GC, 70 eV) *m/z* (%): 307 (25), 290 (80), 290 (12), 256 (56), 229 (10), 154 (26), 127 (49), 75 (15), 51 (10);

HRMS (ESI): calcd. for $C_{18}H_{13}NO_4$ ([M+H]$^+$) 308.09173, found 308.09209.

2-fluoro-9,11-dimethyl-6*H*-chromeno[3,4-*c*]quinolin-6-one (3n):



Starting from compound **2n** (100 mg, 0.28 mmol), the product **3n** was isolated as yellow solid (74 mg, 89 %); mp = 247 – 248 °C;

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.60 (s, 1H, CH_3), 2.78 (s, 1H, CH_3), 7.52 – 7.61 (m, 2H, CH_{Ar}), 7.71 (s, 1H, CH_{Ar}), 8.31 – 8.39 (m, 1H, CH_{Ar}), 8.40 (s, 1H, CH_{Ar}), 9.41 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 17.1 (CH_3), 20.8 (CH_3), 113.0 (C), 113.9 (d, $^{2}J_{C\text{-}F}$ = 26.4 Hz, CH), 117.5 (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz, C), 118.7 (d, $^{2}J_{C\text{-}F}$ = 24.3 Hz, CH), 119.0 (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz, CH), 120.9 (C), 122.2 (CH), 133.9 (2*C, C+CH), 137.1, 137.8 (d, $^{4}J_{C\text{-}F}$ = 2.3 Hz, C), 146.4 (CH), 147.2 (C), 148.3 (d, $^{4}J_{C\text{-}F}$ = 2.0 Hz), 157.8 (d, $^{1}J_{C\text{-}F}$ = 241.3 Hz, C), 158.8 (C=O).

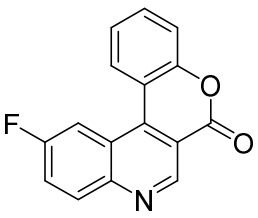
^{19}F NMR (235 MHz, DMSO-d_6): δ = -116.1 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3448 (w), 3133 (w), 3067 (w), 3035 (w), 2960 (w), 2921 (w), 2850 (w), 1926 (w), 1872 (w), 1842 (w), 1743 (m), 1616 (w), 1596 (w), 1574 (m), 1557 (s), 1485 (s), 1454 (m), 1431 (s), 1404 (m), 1385 (m), 1348 (s), 1310 (m), 1282 (m), 1264 (m), 1244 (m), 1207 (m), 1167 (s), 1136 (s), 1107 (s), 1055 (m), 1010 (s), 958 (m), 937 (m), 897 (m), 877 (w), 850 (s), 835 (s), 806 (s), 782 (m), 753 (m), 729 (m), 694 (m), 676 (m), 663 (m), 611 (m), 599 (s), 561 (m), 554 (m);

MS (EI, 70eV): *m/z* (%) = 294 ([M+H]$^{+}$, 20), 293 ([M]$^{+}$, 100), 265 (17), 250 (23);

HRMS (EI) calcd for $C_{18}H_{12}FNO_2$ ([M]$^{+}$) 293.08466, found 293.08497.

11-fluoro-6*H*-chromeno[3,4-*c*]quinolin-6-one (3o):



Starting from compound **2o** (100 mg, 0.3 mmol), the product **3o** was isolated as yellow solid (71 mg, 87 %); mp = 226 – 228 °C;

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.50 – 7.60 (m, 2H, CH_{Ar}), 7.75 (ddd, ^{3}J = 8.0 Hz, ^{3}J = 7.5 Hz, ^{4}J = 1.5 Hz, 1H, CH_{Ar}), 7.88 (ddd, ^{3}J = 9.2 Hz, ^{3}J = 7.9 Hz, ^{4}J = 2.8 Hz, 1H, CH_{Ar}), 8.31 (dd, ^{3}J = 9.2 Hz, ^{3}J = 5.9 Hz, 1H, CH_{Ar}), 8.60 (dd, ^{3}J = 10.9 Hz, ^{4}J = 2.8 Hz, 1H, CH_{Ar}), 8.67 (d, ^{3}J = 8.7 Hz, 1H, CH_{Ar}), 9.46 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 110.93 (d, $^{2}J_{C\text{-}F}$ = 24.9 Hz, CH), 114.4, 116.7 (C), 117.8 (CH), 121.73 (d, $^{2}J_{C\text{-}F}$ = 25.3 Hz, CH), 122.47 (d, $^{3}J_{C\text{-}F}$ = 9.9 Hz, C), 125.2 (CH), 128.2 (CH), 132.6 (CH), 133.20 (d, $^{3}J_{C\text{-}F}$ = 9.6 Hz, CH), 139.6, 147.7 (C), 148.66 (d, $^{4}J_{C\text{-}F}$ = 2.6 Hz, CH), 152.6 (C), 159.3 (C), 161.3 (d, $^{1}J_{C\text{-}F}$ = 248.2 Hz, C).

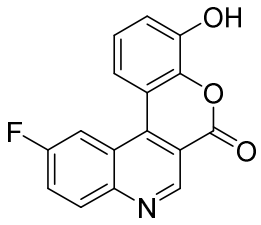
^{19}F NMR (235 MHz, DMSO-d_6): δ = -109.7 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3086 (w), 3055 (w), 2922 (w), 2851 (w), 1737 (s), 1622 (m), 1604 (m), 1593 (s), 1572 (m), 1556 (m), 1511 (s), 1485 (m), 1450 (m), 1440 (m), 1419 (s), 1370 (m), 1354 (s), 1310 (m), 1298 (m), 1207 (s), 1157 (m), 1116 (m), 1086 (s), 1048 (m), 989 (s), 981 (s), 952 (m), 902 (m), 878 (m), 837 (s), 795 (w), 745 (s), 723 (s), 679 (m), 665 (m), 648 (m), 605 (s), 540 (m);

MS (EI, 70eV): *m/z* (%) = 266 ([M+H]$^+$, 17), 265 ([M]$^+$, 100), 264 (14), 237 (40), 209 (11), 208 (24), 182 (17), 181 (20);

HRMS (EI) calcd for $C_{16}H_8FNO_2$ ([M]$^+$) 265.05336, found 365.05347.

11-fluoro-4-hydroxy-6*H*-chromeno[3,4-*c*]quinolin-6-one (3p):



Starting from compound **2p** (100 mg, 0.28 mmol), the product **3p** was isolated as yellow solid (51 mg, 65 %); mp = 282 – 283 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.23 (d, ^{3}J = 7.0 Hz, 1H, CH_{Ar}), 7.31 (t, ^{3}J = 8.1 Hz, 1H, CH_{Ar}), 7.92 (td, ^{3}J = 9.2, ^{4}J = 2.7 Hz, 1H, CH_{Ar}), 8.01 (d, ^{3}J = 7.5 Hz, 1H, CH_{Ar}), 8.24 (dd, ^{3}J = 9.2 Hz, ^{3}J = 6.0 Hz, 1H, CH_{Ar}), 8.52 (dd, ^{3}J = 11.0 Hz, ^{4}J = 2.6 Hz, 1H, CH_{Ar}), 9.40 (s, 1H, CH_{Ar}), 10.36 (s, 1H, OH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 111.3 (d, $^{2}J_{C\text{-}F}$ = 24.9 Hz, CH), 114.25 (C), 117.3 (C), 118.1 (CH), 119.0 (CH), 121.8 (d, $^{2}J_{C\text{-}F}$ = 25.3 Hz, CH), 122.4 (d, $^{3}J_{C\text{-}F}$ = 10.1 Hz, C), 124.9 (CH), 133.0 (d, $^{3}J_{C\text{-}F}$ = 9.5 Hz, CH), 139.95 (d, $^{4}J_{C\text{-}F}$ = 5.1 Hz, C), 141.2 (C), 145.8 (C), 147.3 (C), 148.7 (d, $^{4}J_{C\text{-}F}$ = 2.5 Hz, CH), 159.3 (C=O), 160.9 (d, $^{1}J_{C\text{-}F}$ = 247.4 Hz, C).

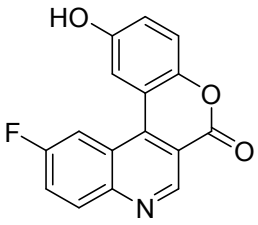
^{19}F NMR (282 MHz, DMSO-d_6): δ = -109.70 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060 (w), 3035 (w), 2946 (w), 2920 (w), 2840 (w), 2727 (w), 1723 (s), 1616 (m), 1577 (s), 1566 (s), 1516 (s), 1436 (s), 1427 (s), 1384 (m), 1362 (s), 1326 (m), 1292 (s), 1209 (s), 1197 (s), 1184 (s), 1156 (m), 1131 (s), 1092 (s), 1054 (s), 995 (s), 952 (m), 901 (m), 873 (s), 853 (s), 812 (m), 796 (s), 773 (s), 765 (s), 750 (s), 721 (s), 665 (m), 649 (m), 634 (m), 600 (m), 568 (m), 562 (m), 545 (m);

MS (EI, 70eV): *m/z* (%) = 282 (18), 281 ([M]$^+$, 100), 253 (25), 225 (22), 197 (25), 196 (21), 170 (14);

HRMS (EI) calcd for $C_{16}H_8FNO_3$ ([M]$^+$) 281.04827, found 281.04837.

11-fluoro-2-hydroxy-6*H*-chromeno[3,4-*c*]quinolin-6-one (3q):



Starting from compound **2q** (100 mg, 0.28 mmol), the product **3q** was isolated as yellow solid (62 mg, 78 %); mp > 350 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.75 (br.s, 1H, OH), 7.2 (dd, ^3J = 8.9 Hz, ^4J = 2.7 Hz, 1H, CH_{Ar}), 7.4 (d, ^3J = 8.9 Hz, 1H, CH_{Ar}), 9.4 (s, 1H, CH_{Ar}), 7.95 (d, ^4J = 2.7 Hz, 1H, CH_{Ar}), 7.97 (dd, ^3J = 2.7 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 8.0 (d, ^4J = 2.6 Hz, 1H, CH_{Ar}), 8.28 (d, ^3J = 6.0 Hz, 1H, CH_{Ar}), 8.3 (d, ^3J = 6.0 Hz, 1H, CH_{Ar}), 8.55 (dd, ^3J = 11.1 Hz, ^4J = 2.7 Hz, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 110.95 (d, $^2J_{C\text{-}F}$ = 24.9 Hz, CH), 112.6 (CH), 114.5, 116.8 (C), 118.95 (CH), 120.7 (CH), 122.05 (d, ^2J = 25.3 Hz, CH), 122.45 (d, $^3J_{C\text{-}F}$ = 10.1 Hz, C), 133.1 (d, ^3J = 9.8 Hz, CH), 139.6 (d, $^4J_{C\text{-}F}$ = 5.1 Hz), 147.1, 145.7 (C), 148.8 (d, $^4J_{C\text{-}F}$ = 2.5 Hz, CH), 154.3 (C), 159.7 (C), 161.05 (d, $^1J_{C\text{-}F}$ = 247.5 Hz, C).

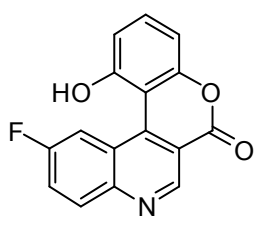
^{19}F NMR (282 MHz, DMSO-d_6): δ = -109.71 (CF).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3073 (m), 3029 (m), 2641 (m), 2598 (m), 1741 (s), 1618 (w), 1580 (s), 1504 (s), 1494 (s), 1445 (s), 1430 (s), 1406 (s), 1359 (s), 1312 (m), 1249 (m), 1235 (s), 1224 (s), 1203 (s), 1138 (s), 1114 (m), 1107 (m), 1019 (m), 987 (s), 935 (w), 878 (s), 863 (s), 836 (s), 781 (s), 753 (m), 734 (s), 666 (s), 599 (s), 530 (m);

MS (EI, 70eV): *m/z* (%) = 282 (39), 281 ([M]$^+$, 100), 253 (42), 225 (19), 224 (13), 197 (16), 196 (18), 171 (10), 170 (14), 169 (13), 78 (17), 63 (21);

HRMS (ESI-TOF) calcd for $C_{16}H_8FNO_3$ ([M+H]$^+$) 282.05610, found 282.05677.

11-fluoro-1-hydroxy-6*H*-chromeno[3,4-*c*]quinolin-6-one (3r):



Starting from compound **2r** (100 mg, 0.28 mmol), the product **3r** was isolated as yellow solid (20 mg, 25 %); mp = 309 – 311 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.00 (d, ^3J = 8.2, 2H, CH_{Ar}), 7.56 (t, ^3J = 8.2 Hz, 1H, CH_{Ar}), 7.88 (ddd, ^3J = 11.8 Hz, ^3J = 8.7 Hz, ^4J = 2.8 Hz, 1H, CH_{Ar}), 8.12 (dd, ^3J = 11.4 Hz,

^4J = 2.8 Hz, 1H, CH_{Ar}), 8.19 (dd, ^3J = 9.2 Hz, ^3J = 5.9 Hz, 1H, CH_{Ar}), 9.40 (s, 1H, CH_{Ar}), 11.29 (s, 1H, OH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 107.4 (CH), 112.7 (CH), 114.5 (d, $^2J_{C\text{-}F}$ = 24.8 Hz, CH), 159.6 (C), 115.0 (C), 121.8 (d, $^2J_{C\text{-}F}$ = 25.4 Hz, CH), 122.5 (d, $^3J_{C\text{-}F}$ = 10.9 Hz), 131.3 (d, $^3J_{C\text{-}F}$ = 9.2 Hz, CH), 133.2 (CH), 140.9 (d, $^4J_{C\text{-}F}$ = 4.9 Hz), 147.0, 147.8 (d, $^4J_{C\text{-}F}$ = 2.3 Hz, CH), 153.4 (C), 155.1 (C), 155.7 (C), 158.6 (d, $^1J_{C\text{-}F}$ = 244.4 Hz);

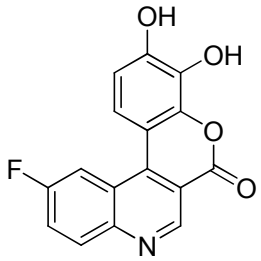
^{19}F NMR (282 MHz, DMSO-d_6): δ = -113.02 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3049 (w), 2927 (w), 2838 (w), 2658 (w), 2538 (w), 1749 (s), 1609 (s), 1594 (s), 1580 (s), 1512 (s), 1457 (s), 1428 (s), 1353 (s), 1299 (s), 1261 (m), 1210 (s), 1195 (s), 1172 (s), 1118 (s), 1087 (s), 1046 (s), 1019 (s), 974 (s), 871 (m), 831 (s), 793 (s), 776 (s), 760 (s), 747 (s), 722 (s), 656 (s), 631 (s), 605 (s), 586 (s), 553 (s), 543 (s);

MS (EI, 70eV): *m/z* (%) = 282 (39), 281 (100), 253 (42), 225 (19), 224 (13), 197 (16), 196 (18), 171 (10), 170 (14), 169 (13), 78 (17), 63 (21);

HRMS (ESI-TOF) calcd for $C_{16}H_8FNO_3$ ($[M+H]^+$) 282.05610, found 282.05653.

11-fluoro-3,4-dihydroxy-6*H*-chromeno[3,4-*c*]quinolin-6-one (3s):



Starting from compound **2s** (100 mg, 0.26 mmol), the product **3s** was isolated as yellow solid (54 mg, 70 %); mp = 321 – 323 °C;

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.62 (broad s, 2H, OH), 7.03 (d, ^3J = 9.0 Hz, 1H, CH_{Ar}), 7.68 – 7.88 (m, 1H, CH_{Ar}), 7.98 (d, ^3J = 9.0 Hz, 1H, CH_{Ar}), 8.14 – 8.44 (m, 1H, CH_{Ar}), 8.52 (dd, ^3J = 11.1 Hz, ^4J = 2.3 Hz, 1H, CH_{Ar}), 9.39 (s, 1H, CH_{Ar});

^{13}C NMR (63 MHz, DMSO-d_6): δ = 108.8 (C), 110.5 (d, $^2J_{C\text{-}F}$ = 24.7 Hz, CH), 111.5 (C), 112.6 (CH), 118.4 (CH), 120.6 (d, $^2J_{C\text{-}F}$ = 25.2 Hz, CH), 121.9 (d, $^3J_{C\text{-}F}$ = 9.5 Hz, C), 132.3 (d, $^3J_{C\text{-}F}$ = 9.5 Hz, CH), 132.8 (C), 140.2 (d, $^4J_{C\text{-}F}$ = 5.1 Hz, C), 142.6 (C), 146.9 (C), 148.2 (d, $^4J_{C\text{-}F}$ = 2.4 Hz, CH), 149.7 (C), 159.0 (C), 160.3 (d, $^1J_{C\text{-}F}$ = 247.6 Hz, C);

^{19}F NMR (235 MHz, DMSO-d_6): δ = -110.81 (CF);

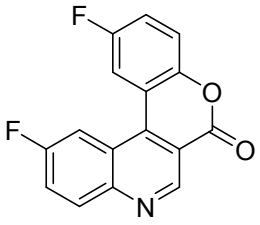
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052 (br.w), 1722 (m), 1715 (m), 1610 (s), 1569 (s), 1508 (s), 1456 (m), 1422 (m), 1345 (s), 1314 (s), 1212 (s), 1191 (s), 1153 (m), 1103 (s),

1074 (s), 1031 (s), 976 (m), 923 (m), 875 (m), 835 (s), 807 (m), 794 (m), 778 (s), 742 (s), 713 (s), 667 (m), 607 (s), 588 (s);

MS (EI, 70eV): *m/z* (%) = 297 (100), 263 (42), 225 (19), 224 (13), 197 (16), 196 (18), 173 (10), 170 (14), 169 (13), 78 (17), 63 (21).

HRMS (ESI): calcd. for $C_{16}H_8FNO_4$ ($[M+H]^+$) 298.05101, found 298.05154;

2,11-difluoro-6*H*-chromeno[3,4-*c*]quinolin-6-one (3t):



Starting from compound **2t** (100 mg, 0.29 mmol), the product **3t** was isolated as yellow solid (70 mg, 85 %); mp = 252 – 254 °C;

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.56– 7.62 (m, 2H, CH_{Ar}), 7.92 (ddd, ^3J = 9.2 Hz, ^3J = 8.0 Hz, ^4J = 2.7 Hz, 1H, CH_{Ar}), 8.30 (dd, ^3J = 9.2 Hz, ^3J = 5.9 Hz, 1H, CH_{Ar}), 8.38 – 8.45 (m, 1H, CH_{Ar}), 8.59 (dd, ^3J = 10.8 Hz, ^4J = 2.7 Hz, 1H, CH_{Ar}), 9.48 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, DMSO): δ = 110.2 (d, $^2J_{C\text{-}F}$ = 25.1 Hz, CH), 113.6 (d, $^2J_{C\text{-}F}$ = 26.4 Hz, CH), 114.0, 117.0 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, C), 119.1 (d, $^3J_{C\text{-}F}$ = 10.1 Hz, CH), 119.2 (d, $^2J_{C\text{-}F}$ = 23.1 Hz, CH), 121.4 (d, $^2J_{C\text{-}F}$ = 25.4 Hz, CH), 121.7 (d, $^3J_{C\text{-}F}$ = 10.3 Hz, C), 132.7 (d, $^3J_{C\text{-}F}$ = 9.6 Hz, CH), 138.1 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, C), 147.1 (d, $^5J_{C\text{-}F}$ = 1.1 Hz, C), 148.0 (d, $^4J_{C\text{-}F}$ = 2.7 Hz, CH), 148.4 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 158.0 (d, $^1J_{C\text{-}F}$ = 242.0 Hz, C), 158.5 (C), 160.8 (d, $^1J_{C\text{-}F}$ = 248.8 Hz, C).

^{19}F NMR (235 MHz, DMSO-d_6): δ = -109.12 (CF), -115.78 (CF).

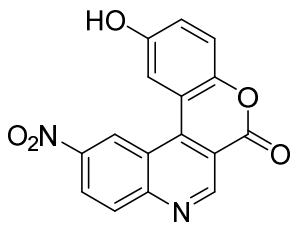
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3140 (w), 3119 (w), 3059 (w), 2987 (w), 1921 (w), 1749 (s), 1620 (m), 1598 (w), 1562 (s), 1511 (s), 1483 (s), 1447 (m), 1422 (s), 1353 (m), 1330 (m), 1310 (m), 1287 (m), 1262 (w), 1232 (m), 1205 (s), 1164 (m), 1151 (m), 1116 (m), 1084 (m), 1005 (s), 987 (s), 965 (m), 890 (w), 859 (s), 838 (s), 822 (s), 812 (m), 790 (w), 753 (m), 742 (s), 727 (m), 709 (s), 682 (m), 662 (m), 648 (m), 605 (m), 596 (s), 547 (w), 526 (s);

MS (EI, 70eV): *m/z* (%) = 284 ($[M+H]^+$, 20), 283 ($[M]^+$, 100), 282 (16), 255 (52), 226 (27), 207 (23), 200 (14), 199 (20), 44 (26), 32 (17);

HRMS (EI) calcd for $C_{16}H_7F_2NO_2$ ($[M]^+$) 283.04394, found 283.04398.

2-hydroxy-11-nitro-6*H*-chromeno[3,4-*c*]quinolin-6-one (3u):

Starting from compound **2u** (100 mg, 0.29 mmol), the product **3u** was isolated as yellow solid (65 mg, 81 %); mp = 300 – 302 °C;



^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.19 (dd, ^3J = 8.9 Hz, ^4J = 2.6 Hz, 1H, CH_{Ar}), 7.42 (d, ^3J = 8.9 Hz, 1H, CH_{Ar}), 7.84 (d, ^4J = 2.6 Hz, 1H, CH_{Ar}), 8.35 (d, ^3J = 9.2 Hz, 1H, CH_{Ar}), 8.65 (dd, ^3J = 9.2 Hz, ^4J = 2.3 Hz, 1H, CH_{Ar}), 9.52 (d, ^4J = 2.2 Hz, 1H, CH_{Ar}), 9.54 (s, 1H, CH_{Ar}), 10.14 (s, 1H, OH).

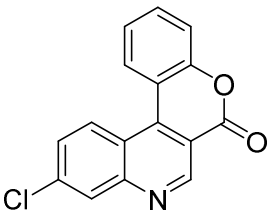
^{13}C NMR (63 MHz, DMSO-d_6): δ = 112.6 (CH), 114.95, 116.4 (C), 119.1 (CH), 120.7 (C), 121.3 (CH), 123.35 (CH), 125.3 (CH), 132.1 (CH), 141.5 (C), 145.95 (C), 146.0 (C), 152.0 (C), 152.7 (CH), 154.5 (C), 159.15 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3323 (w), 3070 (w), 2921 (w), 2850 (w), 2724 (w), 1726 (s), 1693 (s), 1617 (m), 1565 (s), 1530 (m), 1498 (s), 1457 (s), 1435 (s), 1424 (s), 1344 (s), 1302 (s), 1267 (m), 1235 (s), 1218 (s), 1186 (s), 1174 (s), 1131 (m), 1110 (s), 1092 (s), 1013 (s), 972 (m), 935 (m), 914 (m), 860 (s), 845 (s), 835 (s), 822 (s), 796 (m), 739 (s), 711 (s), 694 (s), 663 (s), 629 (s), 603 (s), 596 (s), 546 (s);

MS (EI, 70eV): *m/z* (%) = 309 ([M+H]$^+$, 19), 308 ([M]$^+$, 100), 307 (15), 205 (13), 177 (19);

HRMS (ESI-TOF): calcd. for $C_{16}H_8N_2O_5$ ([M+H]$^+$) 309.05060, found 309.05111.

10-chloro-6*H*-chromeno[3,4-*c*]quinolin-6-one (3v):



Starting from compound **2v** (100 mg, 0.29 mmol), the product **3v** was isolated as yellow solid (68 mg, 83 %); mp = 256 – 257 °C;

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.48 – 7.57 (m, 2H, CH_{Ar}), 7.74 (dd, ^3J = 7.1 Hz, ^3J = 1.3 Hz, 1H, CH_{Ar}), 7.81 (dd, ^3J = 9.3 Hz, ^4J = 2.5 Hz, 1H, CH_{Ar}), 8.18 (d, ^4J = 2.3 Hz, 1H, CH_{Ar}), 8.61 (d, ^3J = 8.4 Hz, 1H, CH_{Ar}), 8.90 (dd, ^3J = 9.2 Hz, ^4J = 0.5 Hz, 1H, CH_{Ar}), 9.46 (s, 1H, CH_{Ar}),

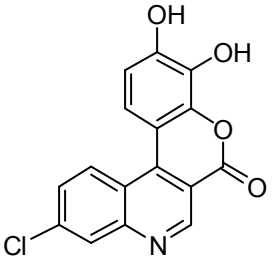
^{13}C NMR (63 MHz, DMSO-d_6): δ = 113.5 (C), 116.0 (C), 117.3 (CH), 119.7 (C), 124.6 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 132.3 (CH), 136.5 (C), 139.7 (C), 149.9 (CH), 150.4 (C), 152.2 (C), 158.6 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3120 (w), 3056 (w), 2991 (w), 2921 (w), 2850 (w), 1727 (s), 1600 (m), 1567 (m), 1553 (s), 1483 (m), 1450 (m), 1401 (m), 1374 (m), 1348 (m), 1300 (m), 1269 (m), 1241 (m), 1220 (m), 1197 (m), 1180 (m), 1159 (m), 1137 (m), 1118 (m), 1079 (s), 1043 (m), 982 (s), 937 (m), 887 (s), 827 (m), 790 (m), 748 (s), 690 (m), 649 (m), 638 (m), 605 (s), 547 (m);

MS (EI, 70eV): *m/z* (%) = 283 (34), 282 (22), 281 ($[M]^+$, 100), 280 (14), 255 (14), 253 (40), 218 (33), 190 (34), 163 (28), 81 (16);

HRMS (EI) calcd for $C_{16}H_8ClNO_2$ ($[M]^+$) 281.02381, found 281.02368.

10-chloro-3,4-dihydroxy-6*H*-chromeno[3,4-*c*]quinolin-6-one (3w):



Starting from compound **2w** (100 mg, 0.269 mmol), the product **3w** was isolated as yellow solid (66 mg, 78 %); mp > 350 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.9 (d, ^3J = 9.0 Hz, 1H, CH_{Ar}), 7.7 (dd, ^3J = 9.2 Hz, ^4J = 2.3 Hz, 1H, CH_{Ar}), 7.8 (d, ^3J = 9.0 Hz, 1H, CH_{Ar}), 8.0 (s, 1H, CH_{Ar}), 8.7 (d, ^3J = 9.2 Hz, 1H, CH_{Ar}), 9.3 (s, 1H, CH_{Ar}), 9.5 (s, 1H), 10.5 (s, 1H, OH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 108.8 (C), 111.7 (C), 112.8 (CH), 119.4 (CH), 120.2 (C), 128.2 (CH), 128.6 (CH), 129.1 (CH), 133.2 (C), 136.55 (C), 141.3 (C), 142.9 (C), 150.3 (C), 150.56 (CH), 150.58 (C), 159.6 (C=O).

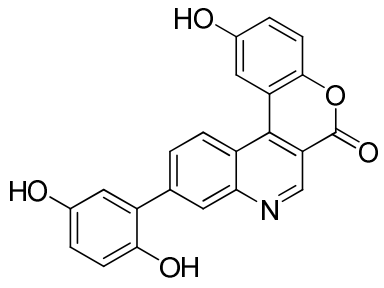
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3571 (m), 3211 (m), 3073 (m), 2920 (m), 2850 (m), 1727 (s), 1713 (s), 1596 (s), 1563 (s), 1515 (s), 1488 (s), 1456 (s), 1395 (s), 1358 (s), 1344 (s), 1300 (s), 1281 (s), 1263 (s), 1196 (s), 1134 (s), 1096 (s), 1062 (s), 1028 (s), 973 (m), 926 (s), 908 (s), 888 (s), 866 (s), 845 (s), 825 (s), 775 (s), 743 (s), 657 (s), 606 (s), 537 (m);

MS (EI, 70eV): *m/z* (%) = 315 (28), 314 (16), 313 ($[M]^+$, 100), 285 (14), 78 (18), 63 (24);

HRMS (EI): calcd. for $C_{16}H_8ClNO_4$ ($[M]^+$) 313.01364, found 313.01303;

HRMS (EI): calcd. for $C_{16}H_8ClNO_4$ ($[M]^+$) 315.01069, found 315.01061.

10-(2,5-dihydroxyphenyl)-2-hydroxy-6*H*-chromeno[3,4-*c*]quinolin-6-one (3x):



Starting from compound **2x** (100 mg, 0.29 mmol), the product **3x** was isolated as yellow solid (50 mg, 72 %); mp > 350 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.09 (br.s, 3H, 3*OH), 6.73 (dd, ^3J = 8.7 Hz, ^4J = 2.9 Hz, 1H, CH_{Ar}), 6.88 (d, ^3J = 8.7 Hz, 1H, CH_{Ar}), 6.93 (d, ^4J = 2.9 Hz, 1H, CH_{Ar}),

7.19 (dd, ^3J = 8.9 Hz, ^4J = 2.7 Hz, 1H, CH_{Ar}), 7.45 (d, ^3J = 8.9 Hz, 1H, CH_{Ar}), 8.12 (dd, ^3J = 8.7 Hz, ^4J = 1.8 Hz, 2H), 8.37 (d, ^4J = 1.8 Hz, 1H, CH_{Ar}), 8.90 (d, ^3J = 9.1 Hz, 1H, CH_{Ar}), 9.50 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 113.2 (CH), 113.5 (C), 116.3 (CH), 116.7 (CH), 117.1 (C), 117.3 (CH), 118.8 (CH), 120.14 (C), 120.5 (CH), 125.8 (C), 126.0 (CH), 129.0 (CH), 130.1 (CH), 140.0 (C), 142.7 (C), 145.8 (C), 147.3 (C), 149.3 (CH), 149.75 (C), 150.4 (C), 154.2 (C), 159.9 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3167 (m), 3093 (m), 2957 (m), 2865 (m), 2700 (m), 2590 (m), 1683 (s), 1593 (s), 1575 (s), 1554 (s), 1493 (s), 1441 (s), 1412 (s), 1379 (s), 1347 (s), 1299 (s), 1242 (s), 1219 (s), 1189 (s), 1168 (s), 1124 (s), 1039 (s), 1022 (s), 945 (m), 892 (m), 876 (m), 808 (s), 799 (s), 778 (s), 751 (s), 687 (s), 664 (s), 654 (s), 607 (s), 550 (s);

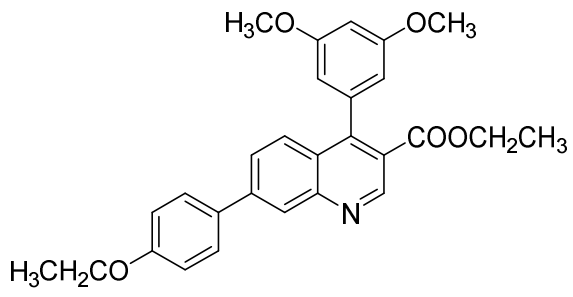
MS (EI, 70eV): *m/z* (%) = 136 (43), 121 ($[M]^+$, 100), 93 (14), 65 (13);

HRMS (ESI-TOF) calcd for $C_{22}H_{13}ClNO_5$ ($[M]^+$) 372.08665, found 372.08648.

General procedure for the synthesis of compounds 5a-n:

To a toluene suspension (4 mL) of **4** (100 mg, 0.37 mmol), $Pd(PPh_3)_4$ (3 mol %), and arylboronic acid (1.1 equiv.) was added K_3PO_4 (238 mg, 1.1 mmol), and the solution was degassed by bubbling argon through the solution for 10 min. The mixture was heated at 70 °C under argon atmosphere for 6 h. The mixture was cooled to 20 °C. To the solution was added arylboronic acid (1.1 equiv.), $Pd(OAc)_2$ (4 mol%), XPhos (8 mol%), and the solution was degassed again. The reaction mixture was heated under argon atmosphere for 8 h at 110 °C. After cooling to 20 °C, the solution was diluted with water and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc).

Ethyl 4-(3,5-dimethoxyphenyl)-7-(4-ethoxyphenyl)quinoline-3-carboxylate (5a):



According to the general procedure compound **5a** was isolated by column chromatography as white crystals (102 mg, 60 %), mp = 161-162 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, ^3J = 7.1 Hz, 3H, CH_3, OCH_2CH_3), 1.45 (t, ^3J = 7.1 Hz, 3H, CH_3, OCH_2CH_3), 3.82 (s, 6H, OCH_3), 4.10 (q, ^3J = 7.1 Hz, 2H, CH_2, OCH_2CH_3), 4.18 (q, ^3J = 7.1 Hz, 2H, CH_2, OCH_2CH_3), 6.47 (d, ^4J = 2.3 Hz, 2H, CH_{Ar}), 6.59 (t, ^4J = 2.3 Hz, 1H, CH_{Ar}), 7.02 (d, ^3J = 8.8 Hz, 2H, CH_{Ar}), 7.69 (d, ^3J = 8.8 Hz, 2H, CH_{Ar}), 7.73-7.78 (m, 2H, CH_{Ar}), 8.35 (s, 1H, CH_{Ar}), 9.33 (s, 1H, CH_{Ar});

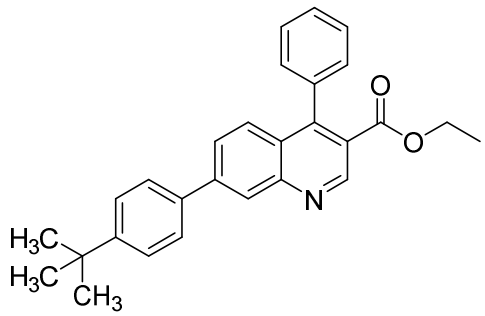
^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 ($COOCH_2CH_3$), 15.0, 55.6 (OCH_3), 61.4, 63.7 ($COOCH_2CH_3$), 100.3 (CH), 107.4 (CH), 115.2 (CH), 122.7 (C), 125.7 (CH), 125.8 (C), 126.8 (CH), 128.1 (CH), 128.7 (CH), 131.8 (C), 138.5 (C), 143.6 (C), 149.4 (C), 149.8 (C), 150.4 (CH), 159.6 (C), 160.7 (C), 166.5 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3008 (w), 2985(w), 2935 (w), 2898 (w), 2844 (w), 1696 (s), 1593 (s), 1579(s), 1521 (m), 1492 (w), 1458 (m), 1407 (m), 1382 (m), 1366 (m), 1345 (w), 1316(m), 1281 (s), 1236 (s), 1188 (s), 1155 (s), 1112 (s), 1049 (s), 1026 (s), 990 (m), 953 (w), 883 (m), 860 (m), 826 (s), 789 (s), 738 (m), 705 (s), 677 (w), 662 (s), 632 (m), 579 (m), 541 (w);

MS (EI, 70 eV) *m/z* (%): 458 ($[M+H]^+$, 33), 457 ($[M]^+$, 100), 357 (11), 29 (17);

HRMS (ESI): calcd for $C_{28}H_{27}NO_5$ 457.18837, found 457.18833.

Ethyl 7-(4-tert-butylphenyl)-4-phenylquinoline-3-carboxylate (5b):



According to the general procedure compound **5b** was isolated by column chromatography as white crystals (95 mg, 62 %), mp = 166-167 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, ^3J = 7.1 Hz, 3H, CH_3, CH_2CH_3), 1.39 (s, 9H, *t*-Bu), 4.13 (q, ^3J = 7.1 Hz, 2H, CH_2, OCH_2CH_3), 7.31-7.35 (m, 2H, CH_{Ar}), 7.51-7.56 (m, 5H, CH_{Ar}), 7.65 (d, ^3J = 8.7 Hz, 1H, CH_{Ar}), 7.71 (d, ^3J = 8.4 Hz, 2H, CH_{Ar}), 7.78 (dd, ^3J = 8.7 Hz, ^4J =1.8 Hz, 1H, CH_{Ar}), 8.43 (d, ^4J = 1.8 Hz, 1H, CH_{Ar}), 9.38 (s, 1H, CH_{Ar});

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.6 (CH_2CH_3), 30.3, 33.7, 60.2 (CH_2CH_3), 123.0 (C), 126.2 (C), 126.2 (CH), 126.5 (CH), 127.0 (CH), 127.3 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 129.0 (CH), 136.7 (C), 136.7 (C), 143.8 (C), 149.4 (C), 150.2 (C), 150.5 (CH), 151.8, 166.6 (C=O);

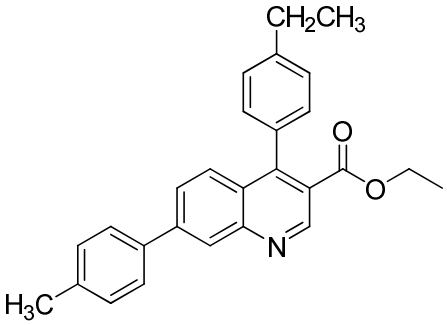
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3058 (w), 2953 (w), 2904 (w), 2865 (w), 1950 (w), 1880 (w), 1703 (s), 1614 (w), 1570 (w), 1484 (w), 1412 (m), 1369 (m), 1325 (m), 1295 (m), 1270 (m), 1221 (s), 1150 (s), 1110 (s), 1025 (m), 943 (w), 911 (m), 867 (w), 845 (m), 820 (s), 798 (s), 768 (m), 700 (s), 587 (m), 565 (m);

MS (EI, 70 eV) *m/z* (%): 410 ($[M+H]^+$, 28), 409 ($[M]^+$, 100);

HRMS (ESI): calcd for $C_{28}H_{27}NO_2$ 409.20363, found 409.20335.

Ethyl 4-(4-ethylphenyl)-7-p-tolylquinoline-3-carboxylate (5c):

According to the general procedure compound **5c** was isolated by column chromatography as white crystals (102 mg, 70 %), mp = 111-112 ºC;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, ^3J = 7.1 Hz, 3H, CH_3, OCH_2CH_3), 1.34 (t, ^3J = 7.6 Hz, 3H, CH_2CH_3), 2.43 (s, 3H, CH_3), 2.78 (q, ^3J = 7.6 Hz, 2H, CH_2CH_3), 4.14 (q, ^3J = 7.1 Hz, 2H, CH_2, OCH_2CH_3), 7.24 (d, ^3J = 8.1 Hz, 2H, CH_{Ar}), 7.32 (d, ^3J = 7.7 Hz, 2H, CH_{Ar}), 7.35 (d, ^3J = 8.3 Hz, 2H, CH_{Ar}), 7.66 (d, ^3J = 8.2 Hz, 2H, CH_{Ar}), 7.70 (d, ^3J = 8.8 Hz, 1H, CH_{Ar}), 7.76 (dd, ^3J = 8.8 Hz, ^4J = 1.7 Hz, 1H, CH_{Ar}), 8.40 (d, ^4J = 1.7 Hz, 1H, CH_{Ar}), 9.35 (s, 1H, CH_{Ar});

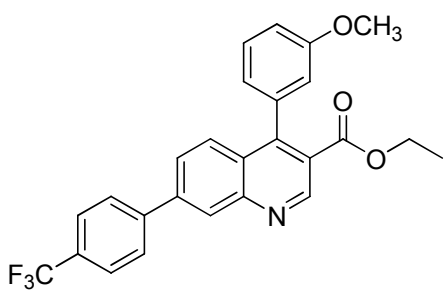
^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 15.7, 21.3, 28.9, 61.3 (CH_2CH_3), 123.2 (C), 126.3 (C), 126.5 (CH), 126.8 (CH), 127.5 (CH), 127.7 (CH), 128.2 (CH), 129.0 (CH), 130.0 (CH), 133.8 (C), 136.9 (C), 138.5 (C), 143.8 (C), 144.5 (C), 149.5 (C), 150.2 (C), 150.5 (CH), 166.8 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3387 (w), 3024 (w), 2955 (w), 2921 (w), 2862 (w), 1904 (w), 1822 (w), 1700 (s), 1615 (m), 1570 (m), 1513 (w), 1487 (w), 1446 (w), 1410 (m), 1365 (m), 1322 (m), 1293 (m), 1250 (m), 1222 (m), 1183 (m), 1149 (m), 1111 (m), 1063 (w), 1052 (w), 1012 (m), 962 (w), 927 (w), 913 (m), 876 (w), 863 (w), 814 (s), 796 (s), 719 (w), 700 (m), 679 (m), 658 (w), 679 (w), 640 (w), 603 (m), 577 (w).

MS (GC, 70 eV) *m/z* (%): 396 ($[M+H]^+$, 27), 395 ($[M]^+$, 100), 350 (27), 322 (13), 307 (12), 29 (19);

HRMS (ESI): calcd. for $C_{27}H_{25}NO_2$ 395.18798, found 395.18766;

Ethyl 4-(3-methoxyphenyl)-7-(4-(trifluoromethyl)phenyl)quinoline-3carboxylate (5d):



According to the general procedure compound **5d** was isolated by column chromatography as white crystals (129 mg, 77 %), mp = 85-86 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, ^3J = 7.1 Hz, 3H, CH_3, CH_2CH_3), 3.85 (s, 3H, OCH_3), 4.16 (q, ^3J = 7.1, 2H,

O*CH*$_2$CH$_3$), 6.87 (dd, ^4J = 2.6 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 6.91 (dt, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, CH_{Ar}), 7.06 (ddd, ^3J = 8.4 Hz, ^4J = 2.6 Hz, ^4J = 1.0 Hz, 1H, CH_{Ar}), 7.44 (dd, ^3J = 8.3 Hz, ^3J = 7.5 Hz, 1H, CH_{Ar}), 7.74-7.78 (m, 4H, CH_{Ar}), 7.86 (d, ^3J = 8.2 Hz, 2H, CH_{Ar}), 8.42 (t, ^4J = 1.2 Hz, 1H, CH_{Ar}), 9.38 (s, 1H, CH_{Ar});

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (OCH$_2$*C*H$_3$), 55.5 (OCH_3), 61.5 (O*C*H$_2$CH$_3$), 114.0 (CH), 114.7 (CH), 121.5 (CH), 123.6 (C), 124.3 (d, $^1J_{C\text{-}F}$ = 234.7 Hz), 126.2 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 126.7 (C), 126.7 (CH), 127.6 (CH), 128.0 (CH), 128.6 (CH), 129.4 (CH), 130.5 (d, $^2J_{C\text{-}F}$ = 32.7 Hz), 137.6 (C), 142.3, 143.3 (d, $^5J_{C\text{-}F}$ = 1.2 Hz, C), 149.2 (C), 149.8 (C), 150.8 (CH), 159.5 (C), 166.4 (C=O);

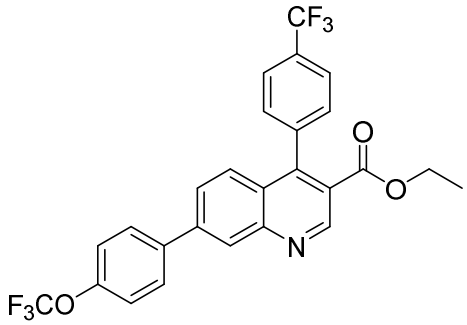
^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.6 (CF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3058 (w), 2956 (w), 2928 (w), 2871 (w), 2835 (w), 1923 (w), 1700 (s), 1612 (w), 1564 (m), 1484 (w), 1470 (w), 1454 (w), 1400 (w), 1369 (w), 1348 (w), 1321 (s), 1284 (m), 1324 (m), 1234 (m), 1208 (m), 1190 (w), 1160 (s), 1150 (s), 1108 (s), 1066 (s), 1044 (s), 1030 (m), 968 (w), 891 (w), 851 (m), 826 (s), 796 (m), 788 (m), 775 (m), 744 (w), 715 (m), 699 (m), 645 (w), 632 (w), 599 (m), 553 (w).

MS (EI, 70 eV) *m/z* (%): 452 ([M+H]$^+$, 28), 451 ([M]$^+$, 100), 407 (25), 406 (71), 379 (14), 378 (13), 376 (10), 364 (13), 363 (12), 335 (19), 334 (13);

HRMS (ESI): calcd for $C_{26}H_{20}FNO_3$ 451.13898, found 451.13885.

Ethyl 7-(4-(trifluoromethoxy)phenyl)-4-(4-(trifluoromethyl)phenyl)quinoline-3-carboxylate (5e):



According to the general procedure compound **5e** was isolated by column chromatography as white crystals (150 mg, 80 %), mp = 124-125 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, ^3J = 7.1 Hz, 3H, CH_3, OCH$_2$C*H*$_3$), 4.16 (q, ^3J = 7.1 Hz, 2H, CH_2, OC*H*$_2$CH$_3$), 7.37 (d, ^3J = 7.9 Hz, 2H, CH_{Ar}), 7.46 (d, ^3J = 8.0 Hz, 2H, CH_{Ar}), 7.55 (d, ^3J = 8.8 Hz, 1H, CH_{Ar}), 7.71-7.86 (m, 5H, CH_{Ar}), 8.41 (d, ^4J = 1.9 Hz, 1H, CH_{Ar}), 9.46 (s, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.7 (CH_2CH_3), 61.6 (*C*H$_2$CH$_3$), 120.6 (d, $^1J_{C\text{-}F}$ = 257.7 Hz, C), 121.7 (CH), 122.8 (C), 124.2 (d, $^1J_{C\text{-}F}$ = 272.0 Hz, C), 125.3 (d, $^5J_{C\text{-}F}$ = 4.3 Hz, CH), 126.0 (C), 127.1 (CH), 127.4 (CH), 128.0 (CH), 129.1 (CH), 129.4

(CH), 130.5 (C), 130.7 (d, $^{2}J_{C\text{-}F}$ = 32.7 Hz, C), 138.2 (C), 140.5 (C), 142.8 (C), 148.6 (C), 149.5 (C), 151.0 (CH), 165.9 (C);

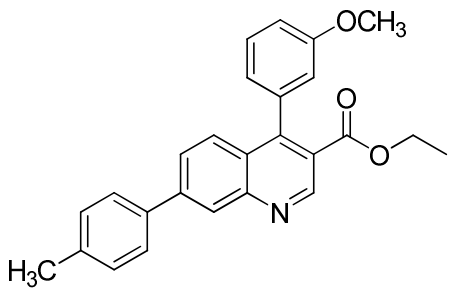
^{19}F NMR (282 MHz, $CDCl_3$) δ = -62.6 (CF_3), -57.8 (OCF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3046 (w), 2995 (w), 2958 (w), 2925 (w), 2852 (w), 1705 (s), 1617 (w), 1588 (w), 1568 (w), 1512 (w), 1489 (w), 1453 (w), 1410 (w), 1370 (w), 1324 (s), 1295 (m), 1254 (s), 1210 (s), 1158 (s), 1152 (s), 1120 (s), 1066 (s), 1021 (s), 960 (m), 923 (m), 851 (m), 831 (s), 796 (s), 764 (m), 718(m), 627 (m), 582 (w).

MS (EI, 70 eV) *m/z* (%): 506 ($[M+H]^+$, 28), 505 ($[M]^+$, 100) , 477 (21), 476 (17), 461 (22), 460 (75), 432 (26), 412 (13), 320 (10), 239 (13), 69 (14);

HRMS (ESI-TOF): calcd for ($[M+H]^+$) $C_{26}H_{17}F_6NO_3$ 506.11854, found 506.11920;

Ethyl 4-(3-methoxyphenyl)-7-p-tolylquinoline-3-carboxylate (5f):



According to the general procedure compound **5f** was isolated by column chromatography as white crystals (129 mg, 88 %), mp = 83-84 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, ^{3}J = 7.1 Hz, 3H, CH_2CH_3), 2.42 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.16 (q, ^{3}J = 7.1 Hz, 2H, CH_2CH_3), 6.87 (dd, ^{4}J = 2.5 Hz, ^{4}J = 1.5 Hz, 1H, CH_{Ar}), 6.91 (ddd, ^{3}J = 7.5 Hz, ^{4}J = 1.6 Hz, ^{4}J = 1.0 Hz, 1H, CH_{Ar}), 7.05 (ddd, ^{3}J = 8.4 Hz, ^{4}J = 2.6 Hz, ^{4}J = 1.0 Hz, 1H, CH_{Ar}), 7.32 (d, ^{3}J = 7.6 Hz, 1H, CH_{Ar}), 7.43 (dd, ^{3}J = 8.3 Hz, ^{3}J = 7.5 Hz, 1H, CH_{Ar}), 7.63-7.72 (m, 3H, CH_{Ar}), 7.71 (s, 1H, CH_{Ar}), 7.77 (dd, ^{3}J = 8.8 Hz, ^{4}J = 1.8 Hz, 1H, CH_{Ar}), 8.40 (d, ^{4}J = 1.8 Hz, 1H, CH_{Ar}), 9.36 (s, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 21.3 (CH_3), 55.5 (OCH_3), 61.3 (CH_2CH_3), 113.9 (CH), 114.7 (CH), 121.5 (CH), 122.9 (C), 126.0 (C), 126.5 (CH), 127.0 (CH), 127.5 (CH), 128.1 (CH), 129.3 (CH), 130.0 (CH), 136.8 (C), 137.9, 138.5 (C), 143.9 (C), 149.4 (C), 149.8 (C), 150.5 (CH), 159.5 (C), 166.5 (C=O);

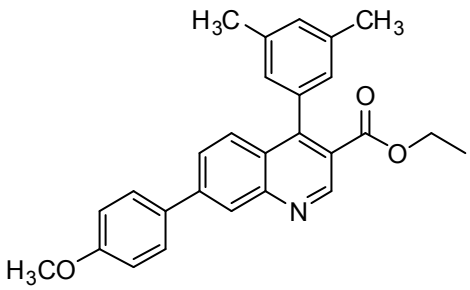
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060 (w), 2982 (w), 2923 (w), 2856 (w), 1699 (s), 1615 (m), 1598 (m), 1585 (m), 1574 (m), 1563 (s), 1480 (m), 1463 (m), 1444 (m), 1425 (m), 1409 (m), 1367 (s), 1324 (s), 1290 (s), 1280 (s), 1269 (s), 1233 (s), 1204 (s), 1174 (s), 1146 (s), 1112 (s), 1079 (s), 1040 (s), 1020 (s), 993 (m), 964 (m), 951 (m), 887 (m),

860 (m), 843 (m), 837 (m), 813 (s), 792 (s), 779 (s), 711 (s), 700 (s), 683 (m), 673 (m), 651 (m), 626 (m), 553 (m), 526 (m);

MS (GC, 70 eV) *m/z* (%): 398 ($[M+H]^+$, 31), 397 ($[M]^+$, 100), 368 (11), 353 (15), 352 (39), 309 (13), 281 (12), 29 (18);

HRMS (EI): calcd. for $C_{26}H_{23}NO_2$ ($[M]^+$) 397.16725, found 397.16794.

Ethyl 4-(3,5-dimethylphenyl)-7-(4-methoxyphenyl)quinoline-3-carboxylate (5g):



According to the general procedure compound **5g** was isolated by column chromatography as white crystals (88 mg, 58 %), mp = 114-115 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 2.40 (s, 6H, 2*CH_3), 3.88 (s, 3H, OCH_3), 4.15 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 6.93 (s, 2H, CH_{Ar}), 7.02 -7.05 (m, 2H, CH_{Ar}), 7.13 (s, 1H, CH_{Ar}), 7.67-7.76 (m, 4H, CH_{Ar}), 8.35 (d, ^4J = 1.8 Hz, 1H, CH_{Ar}), 9.33 (s, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 21.5 (2*CH_3), 55.5 (OCH_3), 61.3 (CH_2CH_3), 114.7 (2*C, CH), 122.9 (C), 125.8 (2*CH), 126.0, 126.7 ((2+1)*C), 128.3 (CH), 128.8 (2*C, CH), 129.9 (CH), 132.1, 136.4 (C), 137.7 (2*C), 143.5 (C), 149.2 (CH), 150.3 (CH), 150.6 (C), 160.2 (C), 166.7 (C=O);

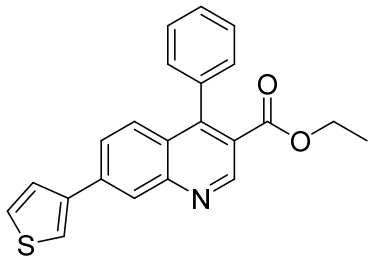
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3041 (w), 2986 (w), 2978 (w), 2964 (w), 2926 (w), 2907 (w), 2859 (w), 2836 (w), 2735 (w), 1895 (w), 1696 (s), 1610 (s), 1602 (m), 1580 (m), 1566 (m), 1559 (m), 1522 (m), 1490 (m), 1476 (m), 1461 (m), 1449 (m), 1439 (m), 1413 (m), 1406 (m), 1368 (s), 1344 (m), 1326 (m), 1288 (s), 1261 (m), 1237 (s), 1199 (s), 1174 (s), 1148 (s), 1127 (s), 1114 (s), 1052 (m), 1035 (s), 1022 (s), 948 (m), 886 (m), 872 (m), 853 (s), 846 (s), 824 (s), 806 (s), 795 (s), 763 (s), 724 (m), 707 (m), 684 (m), 673 (m), 662 (m), 649 (m), 614 (m), 563 (m), 543 (m);

MS (GC, 70 eV) *m/z* (%): 366 ($[M+H]^+$, 31), 365 ($[M]^+$, 100), 366 (25);

HRMS (EI): calcd. for $C_{26}H_{23}NO_2$ ($[M]^+$) 365.05387, found 365.05391.

Ethyl 4-phenyl-7-(thiophen-3-yl)quinoline-3-carboxylate (5h):

According to the general procedure compound **5h** was isolated by column chromatography as white crystals (70 mg, 52 %), mp = 95-96 ºC;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, ^{3}J = 7.1 Hz, 3H, CH_2CH_3), 4.13 (q, ^{3}J = 7.1 Hz, 2H, CH_2CH_3), 7.29 - 7.35 (m, 2H, CH_{Ar}), 7.46 (dd, ^{3}J = 5.1 Hz, ^{4}J = 2.9 Hz, 1H, CH_{Ar}), 7.51-7.53 (m, 3H, CH_{Ar}), 7.57 (dd, ^{3}J = 5.1 Hz, ^{4}J = 1.4 Hz, 1H, CH_{Ar}), 7.62 (d, ^{3}J = 8.8 Hz, 1H, CH_{Ar}), 7.69 (dd, ^{3}J = 3.0 Hz, ^{4}J = 1.4 Hz, 1H, CH_{Ar}), 7.76 (dd, ^{3}J = 8.8 Hz, ^{4}J = 1.8 Hz, 1H, CH_{Ar}), 8.41 (d, ^{4}J = 1.8 Hz, 1H, CH_{Ar}), 9.36 (s, 1H, CH_{Ar});

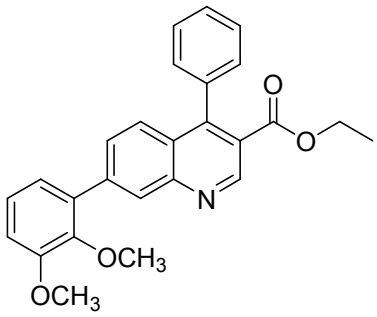
^{13}C NMR (63 MHz, CDCl3): δ = 13.8 (CH_2CH_3), 61.4 (CH_2CH_3), 122.6 (CH), 124.5 (C), 125.7 (CH), 126.4 (CH), 126.4 (CH), 127.1 (CH), 128.2 (2*C, C+CH), 128.3 (CH), 128.9 (CH), 136.6, 138.4, 140.9, 149.4, 150.1, 150.6 (CH), 166.5 (C=O), one Carbon signal cannot be detected;

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3105 (w), 3074 (w), 3054 (w), 2974 (w), 2957 (w), 2923 (w), 2854 (w), 1729 (s), 1697 (s), 1613 (s), 1561 (s), 1525 (m), 1487 (m), 1473 (w), 1455 (w), 1442 (m), 1374 (s), 1333 (m), 1321 (m), 1283 (s), 1260 (s), 1217 (s), 1163 (m), 1151 (m), 1118 (s), 1104 (s), 1072 (m), 1019 (s), 943 (m), 910 (m), 898 (m), 844 (s), 815 (w), 780 (s), 757 (s), 718 (m), 698 (s), 675 (m), 665 (m), 656 (m), 627 (m), 604 (m), 575 (m), 537 (m);

MS (EI, 70 eV) *m/z* (%): 360 ($[M+H]^+$, 25), 359 ($[M]^+$, 100), 331 (13), 315 (18), 314 (71), 286 (29), 285 (12), 284 (11), 258 (18), 241 (10);

HRMS (ESI): calcd for $C_{22}H_{17}NO_2S$ ($[M]^+$) 359.09745, found 359.09777.

Ethyl 7-(2,3-dimethoxyphenyl)-4-phenylquinoline-3-carboxylate (5i):



According to the general procedure compound **5i** was isolated by column chromatography as white crystals (126 mg, 82 %), mp = 117-118 ºC.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.01 (t, ^{3}J = 7.1 Hz, 3H, CH_2CH_3), 3.64 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.13 (q, ^{3}J = 7.1 Hz, 2H, CH_2CH_3), 7.00 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.8 Hz, 1H, CH_{Ar}), 7.09 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.8 Hz, 1H, CH_{Ar}), 7.18 (td, ^{3}J = 7.9 Hz, ^{4}J = 0.7 Hz, 1H, CH_{Ar}), 7.34 (dd, ^{3}J = 6.6 Hz, ^{4}J = 3.0 Hz, 2H, CH_{Ar}), 7.51-7.60 (m, 3H, CH_{Ar}), 7.62 (d, ^{3}J = 8.8 Hz, 1H, CH_{Ar}), 7.77 (dd, ^{3}J = 8.8 Hz, ^{4}J = 1.7 Hz, 1H, CH_{Ar}), 8.33 (d, ^{4}J = 1.7 Hz, 1H, CH_{Ar}), 9.38 (s, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 56.1 (OCH_3), 61.0 (OCH_3), 61.3 (CH_2CH_3), 112.6 (CH), 122.8 (CH), 123.2 (C), 124.6 (CH), 126.2, 127.0 (CH),

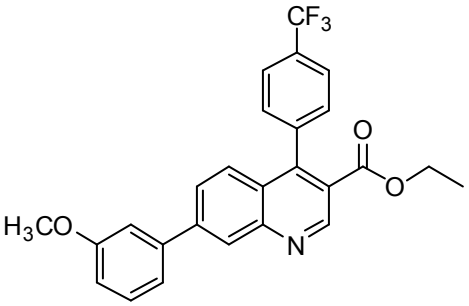
128.2 (CH), 128.3 (CH), 129.0 (CH), 129.1 (CH), 129.6 (CH), 134.6 (C), 136.7 (C), 141.9 (C), 146.9 (C), 149.1 (C), 150.1 (C), 150.2 (CH), 153.3 (C), 166.7 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3057 (w), 2998 (w), 2927 (w), 2900 (w), 2871 (w), 2839 (w), 2820 (w), 1710 (s), 1615 (m), 1596 (w), 1562 (m), 1504 (w), 1491 (w), 1470 (m), 1461 (m), 1437 (m), 1424 (s), 1405 (m), 1402 (m), 1365 (s), 1346 (w), 1328 (w), 1307 (s), 1263 (s), 1245 (s), 1218 (s), 1174 (s), 1150 (s), 1120 (s), 1106 (s), 1089 (s), 1031 (s), 1005 (s), 960 (m), 943 (m), 925 (m), 903 (m), 894 (m), 867 (m), 850 (m), 835 (m), 823 (m), 802 (m), 788 (s), 771 (s), 756 (s), 719 (s), 703 (s), 674 (s), 660 (m), 628 (m), 619 (m), 606 (m), 575 (m), 550 (m), 533 (m);

MS (GC, 70 eV) *m/z* (%): 414 ($[M+H]^+$, 31), 413 ($[M]^+$, 100), 412 (13), 368 (16), 352 (26), 177 (11);

HRMS (EI): calcd. for $C_{26}H_{23}NO_4$ ($[M]^+$) 413.16216, found 413.16189.

Ethyl 7-(3-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)quinoline-3-carboxy-late (5j):



According to the general procedure compound **5j** was isolated by column chromatography as white crystals (142 mg, 85 %), mp = 133-134 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 3.89 (s, 3H, OCH_3), 4.15 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.98 (ddd, ^3J = 8.2 Hz, ^4J = 2.5 Hz, ^4J = 1.0 Hz, 1H, CH_{Ar}), 7.28 (t, ^4J = 2.1 Hz, 1H, CH_{Ar}), 7.33 (dt, ^3J = 7.3 Hz, ^4J = 1.1 Hz, 1H, CH_{Ar}), 7.41 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 7.46 (d, ^3J = 7.3 Hz, 2H, CH_{Ar}), 7.52 (d, ^3J = 8.8 Hz, 1H, CH_{Ar}), 7.76-7.82 (m, 3H, CH_{Ar}), 8.43 (d, ^4J = 1.8 Hz, 1H, CH_{Ar}), 9.45 (s, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_2CH_3), 55.5 (OCH_3), 61.6 (CH_2CH_3), 113.2 (CH), 114.2 (CH), 120.1 (CH), 122.5 (C), 124.2 (d, $^1J_{C-F}$ = 272.3 Hz, C), 125.2 (q, $^3J_{C-F}$ = 3.8 Hz, CH), 125.9 (C), 127.2 (CH), 127.5 (CH), 127.7 (CH), 129.4 (CH), 130.3 (CH), 130.6 (q, $^2J_{C-F}$ = 32.6 Hz, C), 140.6 (d, $^4J_{C-F}$ = 1.2 Hz, C), 140.9 (C), 144.2 (C), 148.6 (C), 149.5 (C), 150.8 (CH), 160.3 (C), 165.9 (C=O);

^{19}F NMR (282 MHz, CDCl3): δ = -62.52 (CF_3).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3100 (w), 3071 (w), 3046 (w), 3000 (w), 2984 (w), 2961 (w), 2917 (w), 2852 (w), 2836 (w), 1936 (w), 1710 (s), 1616 (m), 1606 (m), 1580 (m),

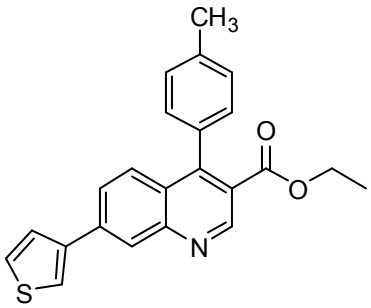
1571 (m), 1564 (m), 1499 (m), 1478 (m), 1460 (m), 1454 (m), 1442 (m), 1422 (m), 1405 (m), 1368 (m), 1345 (m), 1324 (s), 1294 (s), 1284 (s), 1259 (s), 1216 (s), 1207 (s), 1190 (s), 1164 (s), 1147 (s), 1117 (s), 1106 (s), 1067 (s), 1050 (s), 1032 (s), 1022 (s), 962 (m), 950 (m), 937 (m), 915 (m), 904 (m), 880 (m), 865 (s), 844 (s), 836 (s), 819 (s), 801 (s), 774 (s), 750 (s), 718 (s), 696 (s), 681 (s), 664 (s), 650 (m), 630 (s), 622 (s), 599 (m), 568 (m), 532 (m).

MS (GC, 70 eV) *m/z* (%): 452 ($[M+H]^+$, 29), 451 ($[M]^+$, 100), 423 (12), 407 (13), 406 (46), 335 (12).

HRMS (EI): calcd. for $C_{26}H_{20}F_3NO_3$ ($[M]^+$) 451.13898, found 451.13909.

Ethyl 7-(thiophen-3-yl)-4-p-tolylquinoline-3-carboxylate (5k):

According to the general procedure compound **5k** was isolated by column chromatography as white crystals (116 mg, 84 %), mp = 139-140 ºC;



^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 2.48 (s, 3H, CH_3), 4.16 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 7.20 (d, ^3J = 8.0 Hz, 2H, CH_{Ar}), 7.32 (d, ^3J = 8.0 Hz, 2H, CH_{Ar}), 7.45 (dd, ^3J = 5.0 Hz, ^3J = 2.9 Hz, 1H, CH_{Ar}), 7.57 (dd, ^3J = 5.0 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.66 (d, ^3J = 8.8 Hz, 1H, CH_{Ar}), 7.68 (dd, ^3J = 2.9 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.75 (dd, ^3J = 8.8 Hz, ^4J = 2.0 Hz, 1H, CH_{Ar}), 8.40 (d, ^4J = 2.0 Hz, 1H, CH_{Ar}), 9.33 (s, 1H, CH_{Ar});

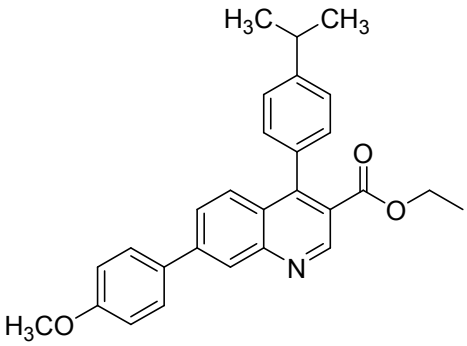
^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 21.4 (CH_3), 61.2 (CH_2CH_3), 122.4 (CH), 123.0 (C), 125.7 (CH), 126.2 (CH), 126.3 (2*C, C+CH), 126.9 (CH), 128.1 (CH), 128.8 (CH), 128.8 (CH), 133.4 (C), 138.0 (C), 138.1 (C), 140.9 (C), 149.4 (C), 150.5 (CH), 166.5 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3108 (w), 3084 (w), 3068 (w), 3038 (w), 2984 (w), 2955 (w), 2921 (w), 2852 (w), 1696 (s), 1615 (s), 1575 (s), 1530 (w), 1514 (w), 1493 (m), 1474 (w), 1147 (m), 1416 (m), 1409 (m), 1373 (s), 1337 (w), 1320 (s), 1281 (s), 1261 (s), 1249 (s), 1218 (s), 1210 (s), 1194 (s), 1175 (s), 1148 (s), 1119 (s), 1110 (s), 1090 (s), 1025 (s), 1014 (s), 948 (m), 910 (w), 884 (s), 875 (m), 843 (s), 838 (s), 817 (m), 787 (s), 724 (m), 710 (m), 697 (m), 681 (m), 668 (m), 659 (m), 631 (m), 616 (m), 608 (m), 588 (m), 559 (m), 528 (m);

MS (GC, 70 eV) *m/z* (%): 374 ($[M+H]^+$,26), 373 ($[M]^+$, 100), 345 (11), 344 (11), 329 (18), 328 (69), 300 (18), 299 (13);

HRMS (EI): calcd. for $C_{23}H_{19}NO_2S$ ($[M]^+$) 373.11310, found 373.11233.

Ethyl 4-(4-isopropylphenyl)-7-(4-methoxyphenyl)quinoline-3-carboxylate (5l):



According to the general procedure compound **5l** was isolated by column chromatography as white crystals (133 mg, 85 %), mp = 166-167 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, ^3J = 7.1 Hz, 3H, CH_3, OCH_2CH_3), 1.35 (d, ^3J = 6.9 Hz, 6H, $CH(CH_3)_2$), 3.03 (hept, ^3J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.87 (s, 3H, OCH_3), 4.11 (q, ^3J = 7.1 Hz, 2H, CH_2, OCH_2CH_3), 7.04 (d, ^3J = 8.8 Hz, 2H, CH_{Ar}), 7.24 (d, ^3J = 8.2 Hz, 2H, CH_{Ar}), 7.37 (d, ^3J = 8.1 Hz, 2H, CH_{Ar}), 7.69-7.74 (m, 4H, CH_{Ar}), 8.36 (d, ^4J = 1.1 Hz, 1H, CH_{Ar}), 9.33 (s, 1H, CH_{Ar});

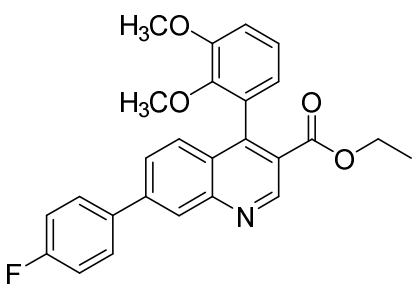
^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.5 (CH_2CH_3), 24.0 ($CH(CH_3)_2$), 34.0 ($CH(CH_3)_2$), 55.4 (OCH_3), 61.1 (CH_2CH_3), 114.7 (CH), 123.2 (C), 126.0 (CH), 126.0 (C), 126.3 (CH), 126.7 (CH), 128.2 (CH), 128.7 (CH), 129.0 (CH), 132.1 (C), 134.0, 143.4 (C), 149.1 (C), 149.4 (C), 150.2 (C), 150.5 (CH), 160.2, 167.0 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3382 (w), 3051 (w), 2960 (w), 2949 (w), 2923 (w), 2866 (w), 1909 (w), 1880 (w), 1851 (w), 1699 (s), 1605 (m), 1572 (m), 1561 (m), 1511 (m), 1487 (m), 1449 (m), 1439 (m), 1379 (m), 1364 (m), 1324 (m), 1301 (s), 1250 (s), 1217 (s), 1187 (m), 1172 (s), 1152 (m), 1127 (m), 1110 (s), 1037 (s), 1020 (s), 992 (m), 952 (w), 941 (m), 931 (w), 886 (m), 869 (m), 849 (w), 834 (s), 823 (s), 800 (s), 769 (m), 758 (m), 739 (m), 693 (m), 679 (s), 657 (m), 599 (m), 564 (m), 556 (m), 536 (m);

MS (EI, 70 eV) *m/z* (%): 426 ($[M+H]^+$, 29), 425 ($[M]^+$, 100), 338 (17);

HRMS (ESI): calcd for $C_{26}H_{20}FNO_3$ 425.19855, found 425.19774;

Ethyl 4-(2,3-dimethoxyphenyl)-7-(4-fluorophenyl)quinoline-3-carboxylate (5m):



According to the general procedure compound **5m** was isolated by column chromatography as white crystals (81 mg, 51 %), mp = 133-136 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 3.96 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 4.19 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.74 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, CH_{Ar}), 7.08 (dd, ^3J = 8.3 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.13

– 7.24 (m, 3H, CH_{Ar}), 7.64 (dd, ^3J = 8.8 Hz, ^4J = 0.4 Hz, 1H, CH_{Ar}), 7.70 (dt, ^3J = 8.8 Hz, ^4J = 3.5 Hz, 3H, CH_{Ar}), 8.34 (d, ^4J = 1.4 Hz, 1H, CH_{Ar}), 9.43 (s, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.7 (CH_2CH_3), 55.8 (OCH_3), 60.5 (OCH_3), 61.1 (CH_2CH_3), 112.6 (CH), 116.0 (d, $^2J_{C\text{-}F}$ = 21.6 Hz, CH), 121.8 (CH), 123.0 (C), 123.9 (CH), 126.1 (C), 126.7 (CH), 126.9 (CH), 128.2 (CH), 129.3 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, CH), 131.0, 135.9 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 142.6 (C), 146.2, 147.1, 149.4 (C), 150.9 (CH), 152.7 (C), 163.0 (d, $^1J_{C\text{-}F}$ = 248.1 Hz, C), 166.2 (C=O);

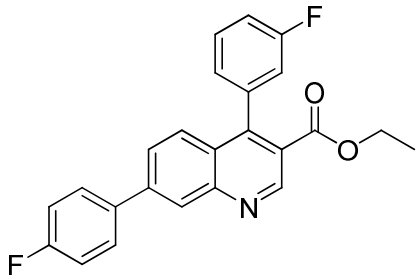
^{19}F NMR (282 MHz, $CDCl_3$): δ = -113.84 (CF).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3062 (w), 2970 (w), 2933 (w), 2829 (w), 1701 (s), 1616 (w), 1601 (w), 1571 (m), 1516 (m), 1496 (m), 1469 (s), 1450 (w), 1441 (w), 1427 (w), 1414 (w), 1399 (w), 1380 (w), 1366 (w), 1345 (w), 1324 (w), 1293 (s), 1261 (s), 1219 (s), 1191 (s), 1171 (s), 1151 (s), 1130 (s), 1107 (s), 1077 (s), 1012 (s), 1003 (s), 940 (m), 912 (m), 899 (m), 863 (m), 840 (m), 825 (s), 812 (s), 795 (s), 771 (s), 751 (s), 720 (m), 700 (m), 678 (m), 608 (m), 554 (m);

MS (EI, 70 eV) *m/z* (%): 432 ($[M+H]^+$, 30), 431 ($[M]^+$, 100), 400 (22), 386 (16), 373 (18), 372 (67), 371 (10), 356 (14), 343 (16), 329 (12), 328 (14), 300 (20), 280 (26), 272 (11), 271 (11), 29 (36);

HRMS (EI): calcd for ($[M]^+$) $C_{26}H_{17}F_6NO_3$ 431.15274, found 431.15223;

Ethyl 4-(3-fluorophenyl)-7-(4-fluorophenyl)quinoline-3-carboxylate (5n):



According to the general procedure compound **5n** was isolated by column chromatography as white crystals (82 mg, 57 %), mp = 96-98 ºC;

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.10 (t, ^3J = 7.1 Hz, 3H, CH_3, CH_2CH_3), 4.18 (q, ^3J = 7.1 Hz, 2H, CH_2, CH_2CH_3), 7.06-7.17 (m, 1H, CH_{Ar}), 7.19-7.36 (m, 4H, CH_{Ar}), 7.41-7.58 (m, 3H, CH_{Ar}), 7.64 (dd, ^3J = 8.8 Hz, J = 0.6 Hz, 1H, CH_{Ar}), 7.74 (dd, ^3J = 8.8 Hz, ^4J = 1.9 Hz, 1H, CH_{Ar}), 8.40 (d, ^4J = 1.7 Hz, 1H, CH_{Ar}), 9.40 (s, 1H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 61.4 (CH_2CH_3), 114.4 (d, $^2J_{C\text{-}F}$ = 22.4 Hz, CH), 115.0 (d, ^1J = 21.1 Hz, CH), 115.3 (d, $^1J_{C\text{-}F}$ = 22.0 Hz, CH), 123.1 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, CH), 123.3 (C), 126.5 (C), 126.7 (CH), 127.4 (CH), 127.9 (CH), 130.6 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, CH), 130.6 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, CH), 132.2 (d,

$^4J_{C\text{-}F}$ = 3.7 Hz, C), 141.8 (d, $^3J_{C\text{-}F}$ = 7.3 Hz, C), 142.4 (d, $^4J_{C\text{-}F}$ = 2.3 Hz, C), 148.6 (C), 149.4 (C), 150.8 (CH), 162.8 (d, $^1J_{C\text{-}F}$ = 247.7 Hz, C), 163.3 (d, $^1J_{C\text{-}F}$ = 246.7 Hz, C), 166.3 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3057 (w), 2979 (m), 2926 (w), 2900 (w), 2867 (w), 1702 (s), 1608 (m), 1501 (s), 1291 (m), 1218 (s), 1018 (m), 782 (vs), 696 (m), 556 (m).

MS (GC-MS): m/z (%) = 390 ($[M+H]^+$, 26), 389 ($[M]^+$ 100), 361 (20), 360 (11), 345 (23), 344 (83), 317 (12), 316 (42), 315 (16), 314 (14), 288 (29).

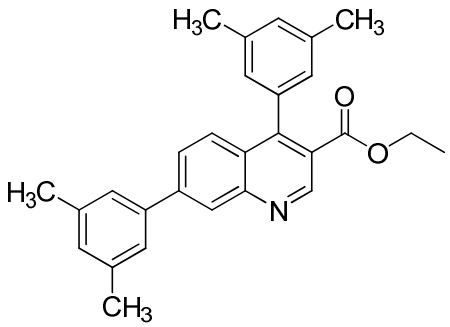
HRMS (EI): calcd for ($[M]^+$) $C_{24}H_{17}F_2NO_2$ 389.12219, found 389.12194;

General procedure for the synthesis of compounds 6a-j:

To a toluene suspension (4 mL) of **4** (100 mg, 0.37 mmol), arylboronic acid (2.2 equiv.), $Pd(OAc)_2$ (3.3 mg, 4 mol %), XPhos (14 mg, 8 mol %), K_3PO_4 (2.5 equiv) and was degassed by bubbling argon through the solution for 10 min. The reaction mixture was heated under argon atmosphere for 8 h at 110 °C. After cooling to 20 °C, the solution was diluted with water and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc).

Ethyl 4,7-bis(3,5-dimethylphenyl)quinoline-3-carboxylate (6a):

According to the general procedure compound **6a** was isolated by column chromatography as white crystals (147 mg, 97 %), mp = 115-117 ºC



^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, ^3J = 7.1, 3H, CH_2CH_3), 2.40 (s, 6H, 2*CH_3), 2.42 (s, 6H, 2*CH_3), 4.16 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.94 (s, 2H, CH_{Ar}), 7.07 (s, 1H, CH_{Ar}), 7.13 (s, 1H, CH_{Ar}), 7.38 (s, 2H, CH_{Ar}), 9.34 (s, 1H, CH_{Ar}), 7.70 (d, ^3J = 8.8 Hz, 1H, CH_{Ar}), 7.76 (dd, ^3J = 8.8 Hz, ^4J = 1.8 Hz, 1H, CH_{Ar}), 8.39 (d, ^4J = 1.8 Hz, 1H, CH_{Ar});

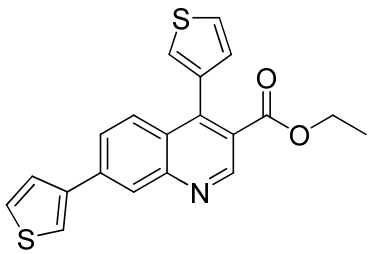
^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.7 (CH_2CH_3), 21.3 (CH_3), 21.4 (CH_3), 61.1 (CH_2CH_3), 123.0 (C), 125.4 (CH), 126.2 (C), 126.55 (CH), 126.6 (CH), 126.95 (CH), 128.05 (CH), 129.8 (CH), 130.0 (CH), 136.2 (C), 137.6 (C), 138.6 (C), 139.6 (C), 144.1 (C), 149.0 (C), 150.15 (CH), 150.4 (C), 166.6 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2975 (w), 2917 (m), 2858 (w), 2731 (w), 1705 (s), 1615 (m), 1601 (s), 1566 (s), 1498 (w), 1444 (m), 1402 (m), 1367 (s), 1344 (m), 1303 (s), 1269 (s), 1236 (s), 1209 (s), 1192 (s), 1150 (s), 1119 (s), 1079 (w), 1048 (s), 1016 (m), 942 (w), 890 (m), 851 (s), 831 (s), 798 (s), 778 (m), 762 (w), 706 (s), 679 (w), 662 (m), 653 (s), 600 (w), 577 (w), 540 (w);

MS (GC, 70 eV) *m/z* (%): 410 (31), 409 ($[M]^+$, 100), 380 (13), 365 (12), 364 (41), 321 (11), 29 (17);

HRMS (EI): calcd. for $C_{28}H_{27}NO_2$ ($[M]^+$) 409.20363, found 409.20372.

Ethyl 4,7-di(thiophen-3-yl)quinoline-3-carboxylate (6b):



According to the general procedure compound **6b** was isolated by column chromatography as white crystals (127 mg, 94 %), mp = 94-95 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 4.19 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 7.15 (dd, ^3J = 4.9 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.31 (dd, ^4J = 3.0 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.46 (dd, ^3J = 5.0 Hz, ^4J = 2.9 Hz, 1H, CH_{Ar}), 7.51 (dd, ^3J = 4.9 Hz, ^4J = 2.9 Hz, 1H, CH_{Ar}), 7.57 (dd, ^3J = 5.1 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 7.69 (dd, ^4J = 2.9 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 7.74 (d, ^3J = 8.8 Hz, 1H, CH_{Ar}), 7.79 (dd, ^3J = 8.8 Hz, ^4J = 1.7 Hz, 1H, CH_{Ar}), 8.39 (d, ^4J = 1.7 Hz, 1H, CH_{Ar}), 9.30 (s, 1H, CH_{Ar});

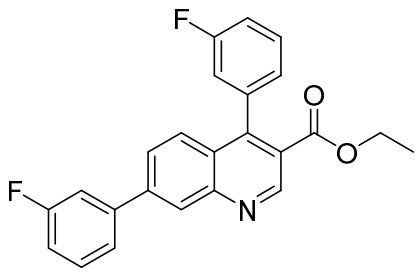
^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 61.5 (CH_2CH_3), 122.6 (CH), 123.8 (C), 124.5 (CH), 125.7 (CH), 125.8 (CH), 126.4 (CH), 126.5 (CH), 126.5 (C), 127.1 (CH), 127.9 (CH), 129.2 (CH), 136.0 (C), 138.4 (C), 140.9 (C), 145.1 (C), 149.5 (C), 150.4 (CH), 166.7 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3394 (w), 3101 (w), 3075 (w), 2981 (w), 2958 (w), 2923 (w), 2851 (w), 1704 (s), 1615 (m), 1569 (s), 1527 (m), 1494 (w), 1479 (w), 1470 (w), 1446 (m), 1424 (m), 1391 (w), 1374 (m), 1364 (m), 1352 (m), 1317 (s), 1281 (s), 1248 (s), 1221 (s), 1206 (m), 1190 (s), 1170 (s), 1147 (s), 1111 (s), 1089 (m), 1070 (m), 1020 (s), 1005 (m), 959 (w), 948 (w), 877 (w), 860 (m), 844 (s), 824 (s), 800 (s), 769 (s), 704 (m), 687 (s), 665 (s), 636 (m), 614 (m), 606 (m), 596 (m), 566 (m), 535 (m);

MS (GC, 70 eV) *m/z* (%): 365 ($[M]^+$, 100), 337 (16), 336 (19), 321 (22), 320 (59), 293 (12), 292 (32), 291 (13), 264 (15), 247 (10), 45 (16), 29 (28);

HRMS (EI): calcd. for $C_{20}H_{15}NO_2S_2$ ($[M]^+$) 365.05387, found 365.05331;

Ethyl 4,7-bis(3-fluorophenyl)quinoline-3-carboxylate (6c):



According to the general procedure compound **6c** was isolated by column chromatography as white crystals (124 mg, 86 %), mp = 102-103 ºC;

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.1 (t, ^{3}J = 7.2 Hz, 3H, CH_2CH_3), 4.2 (q, ^{3}J = 7.1 Hz, 2H, CH_2CH_3), 7.00 – 7.17 (m, 3H, CH_{Ar}), 7.18 – 7.26 (m, 1H, CH_{Ar}), 7.38-7.58 (m, 4H,CH_{Ar}), 7.63 (dd, ^{3}J = 8.8 Hz, ^{4}J = 0.6 Hz, 1H, CH_{Ar}), 7.74 (dd, ^{3}J = 8.8 Hz, ^{4}J = 1.9 Hz, 1H, CH_{Ar}), 8.39 (d, ^{4}J = 1.9 Hz, 1H, CH_{Ar}), 9.41 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 61.5(CH_2CH_3), 114.5 (d, $^{2}J_{C\text{-}F}$ = 22.3 Hz, CH), 115.3 (d, $^{4}J_{C\text{-}F}$ = 1.8 Hz, CH), 115.4 (d, $^{4}J_{C\text{-}F}$ = 2.0 Hz, CH), 116.3 (d, $^{2}J_{C\text{-}F}$ = 22.5 Hz, CH), 123.1 (C), 123.3 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz, CH), 124.8 (d, $^{4}J_{C\text{-}F}$ = 3.1 Hz, CH), 126.2 (C), 126.9 (CH), 127.5 (CH), 128.0 (CH), 130.0 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz, CH), 130.8 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz, C), 138.7 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz, CH), 141.9 (d, $^{3}J_{C\text{-}F}$ = 7.7 Hz, C), 142.6 (d, $^{4}J_{C\text{-}F}$ = 2.3 Hz), 148.3 (d, $^{4}J_{C\text{-}F}$ = 2.0 Hz), 149.6 (C), 151.0 (CH), 162.7 (d, $^{1}J_{C\text{-}F}$ = 247.4 Hz, C), 163.4 (d, $^{1}J_{C\text{-}F}$ = 246.5 Hz, C), 166.2 (C=O);

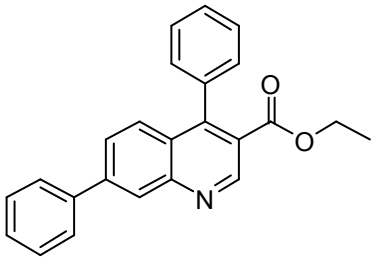
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3044 (w), 2979 (w), 2929 (w), 2909 (w), 2869 (w), 1704 (s), 1612 (s), 1582 (m), 1564 (s), 1489 (m), 1479 (m), 1431 (s), 1404 (m), 1381 (m), 1366 (m), 1345 (m), 1325 (m), 1292 (s), 1265 (s), 1225 (s), 1203 (s), 1173 (s), 1156 (s), 1140 (s), 1117 (s), 1073 (m), 1044 (m), 1018 (s), 1001 (m), 943 (m), 933 (m), 897 (s), 865 (s), 837 (m), 822 (s), 800 (s), 780 (s), 716 (s), 700 (s), 692 (s), 674 (s), 653 (s), 636 (m), 603 (m), 584 (m), 546 (w);

MS (GC, 70 eV) *m/z* (%): 390 (28), 389 ($[M]^+$, 100), 361 (21), 344 (81), 317 (12), 316 (51), 315 (18), 314 (19), 296 (11), 286 (13), 268 (10), 29 (31);

HRMS (EI): calcd. for $C_{24}H_{17}F_2NO_2$ ($[M]^+$) 389.12219, found 389.12199.

Ethyl 4,7-diphenylquinoline-3-carboxylate (6d):

According to the general procedure compound **6d** was isolated by column chromatography as white crystals (115 mg, 88 %), mp = 104-105 ºC;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, ^{3}J = 7.1 Hz, 3H, CH_2CH_3), 4.13 (q, ^{3}J = 7.1 Hz, 2H, CH_2CH_3), 7.3 – 7.36 (m, 2H, CH_{Ar}), 7.40 – 7.46 (m, 1H, CH_{Ar}), 7.47 – 7.55 (m, 5H, CH_{Ar}), 7.66 (d, ^{3}J = 8.8 Hz, 1H, CH_{Ar}), 7.73 – 7.8 (m, 3H, CH_{Ar}), 8.41 (d, ^{4}J = 1.6 Hz, 1H, CH_{Ar}), 9.38 (s, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 61.3 (CH_2CH_3), 123.1 (C), 126.3 (C), 126.9 (CH), 127.2 (CH), 127.6 (CH), 128.2 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 129.0 (CH), 129.2 (CH), 136.7 (C), 139.8 (C), 143.8 (C), 149.7 (C), 149.8 (C), 150.8 (CH), 166.7 (C=O);

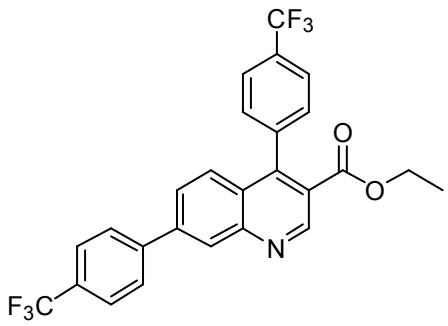
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3055 (w), 3042 (w), 2987 (w), 2925 (w), 2908 (w), 2870 (w), 2854 (w), 1705 (s), 1614 (m), 1599 (m), 1579 (m), 1562 (m), 1482 (m), 1470 (m), 1444 (m), 1434 (m), 1402 (m), 1365 (s), 1322 (s), 1292 (s), 1276 (s), 1261 (s), 1242 (s), 1214 (s), 1186 (s), 1176 (s), 1159 (s), 1119 (s), 1110 (s), 1073 (s), 1017 (s), 972 (m), 966 (m), 951 (m), 941 (m), 922 (w), 892 (s), 863 (s), 838 (s), 802 (s), 761 (s), 724 (s), 709 (s), 697 (s), 675 (s), 649 (m), 628 (s), 615 (s), 573 (s), 543 (m), 535 (m);

MS (GC, 70 eV) *m/z* (%): 354 (27), 353 ($[M]^+$, 100), 325 (12), 324 (10), 309 (20), 308 (64), 280 (32), 279 (15), 278 (18), 252 (23), 250 (15);

HRMS (EI): calcd. for $C_{24}H_{19}NO_2$ ($[M]^+$) 353.14103, found 353.14092.

Ethyl 4,7-bis(4-(trifluoromethyl)phenyl)quinoline-3-carboxylate (6e):

According to the general procedure compound **6e** was isolated by column chromatography as white crystals (100 mg, 56 %), mp = 155-156 ºC;



H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, ^{3}J = 7.1 Hz, 3H, CH_2CH_3), 4.16 (q, ^{3}J = 7.2 Hz, 2H, CH_2CH_3), 7.42 – 7.52 (m, 2H, CH_{Ar}), 7.58 (d, ^{3}J = 8.8 Hz, 1H, CH_{Ar}), 7.72 – 7.90 (m, 7H, CH_{Ar}), 8.45 (d, ^{4}J = 1.8 Hz, 1H, CH_{Ar}), 9.46 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.7 (CH_2CH_3), 61.6(CH_2CH_3), 123.0 (C), 124.2 (d, $^{1}J_{C\text{-}F}$ = 272.2 Hz, C), 124.2 (d, $^{1}J_{C\text{-}F}$ = 272.1 Hz, C), 125.3 (q, $^{2}J_{C\text{-}F}$ = 3.7 Hz, CH), 126.2 (q, $^{2}J_{C\text{-}F}$ = 3.7, CH), 126.3, 127.0 (CH), 127.95 (CH), 128.0 (CH), 128.1 (CH), 129.4 (CH), 130.6 (d, $^{3}J_{C\text{-}F}$ = 32.7 Hz, C), 130.8 (d, $^{3}J_{C\text{-}F}$ = 32.6 Hz, C), 140.5 (d,

$^{5}J_{C\text{-}F}$ = 1.2 Hz), 142.6, 143.1 (d, $^{5}J_{C\text{-}F}$ = 1.1 Hz), 148.5, 149.5 (C), 151.2 (CH), 165.9 (C=O);

^{19}F NMR (282 MHz, CDCl3): δ = -62.55 (CF_3), -62.60 (CF_3);

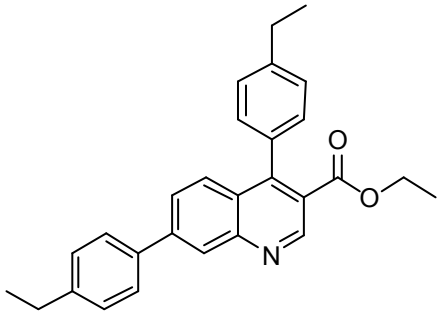
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3047 (w), 2994 (w), 2942 (w), 2908 (w), 1705 (s), 1614 (m), 1568 (m), 1491 (w), 1477 (w), 1453 (w), 1443 (w), 1409 (m), 1400 (m), 1370 (m), 1322 (s), 1299 (s), 1265 (m), 1245 (m), 1223 (m), 1191 (m), 1162 (s), 1155 (s), 1118 (s), 1107 (s), 1066 (s), 1021 (s), 1011 (s), 993 (m), 956 (m), 949 (m), 931 (m), 887 (m), 876 (m), 866 (m), 851 (s), 828 (s), 820 (s), 798 (s), 778 (m), 764 (s), 743 (m), 718 (s), 676 (m), 652 (m), 642 (m), 631 (m), 598 (s), 575 (m), 537 (m);

MS (EI, 70 eV) *m/z* (%): 490 (29), 489 ([M]$^{+}$, 100), 470 (14), 461 (29), 460 (13), 445 (27), 444 (92), 417 (37), 416 (38), 415 (11), 396 (22), 346 (11), 320 (18), 69 (12), 29 (33);

HRMS (ESI-TOF): calcd. for $C_{26}H_{17}F_6NO_2$ ([M+H]$^{+}$) 490.12362, found 490.12413.

Ethyl 4,7-bis(4-ethylphenyl)quinoline-3-carboxylate (6f):

According to the general procedure compound **6f** was isolated by column chromatography as white crystals (126 mg, 83 %), mp = 122-123 ºC;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, ^{3}J = 7.1 Hz, 3H, OCH_2CH_3), 1.30 (t, ^{3}J = 7.6 Hz, 3H, CH_3), 1.34 (t, ^{3}J = 7.6 Hz, 3H, CH_3), 2.73 (q, ^{3}J = 7.7 Hz, 2H, CH_2), 2.79 (q, ^{3}J = 7.7 Hz, 2H, CH_2), 4.14 (q, ^{3}J = 7.1 Hz, 2H, OCH_2CH_3), 7.24 (d, ^{3}J = 8.1 Hz, 2H, CH_{Ar}), 7.35 (d, ^{3}J = 8.0 Hz, 4H, CH_{Ar}), 7.64–7.73 (m, 3H, CH_{Ar}), 7.76 (dd, ^{3}J = 8.8 Hz, ^{4}J = 1.8 Hz, 1H, CH_{Ar}), 8.40 (d, ^{3}J = 1.8 Hz, 1H, CH_{Ar}), 9.35(s, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 15.6 (CH_3), 15.7 (CH_3), 28.7 (CH_2), 28.9 (CH_2), 61.27 (CH_2CH_3), 123.2 (C), 126.3 (C), 126.6 (CH), 126.9 (CH), 127.55 (CH), 127.7 (CH), 128.2 (CH), 128.8 (CH), 128.96 (CH), 133.8 (C), 137.1 (C), 143.8 (C), 144.45 (C), 144.8 (C), 149.45 (C), 150.2 (C), 150.5 (CH), 166.8 (C=O);

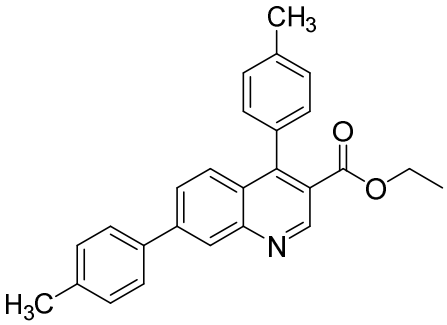
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3045 (w), 3019 (w), 2959 (w), 2924 (w), 2905 (w), 2864 (w), 1910 (w), 1889 (w), 1704 (s), 1614 (m), 1571 (m), 1513 (m), 1488 (m), 1460 (m), 1449 (m), 1411 (m), 1404 (m), 1366 (m), 1346 (m), 1321 (m), 1292 (m), 1274 (m),

12631249 (m), 1221 (s), 1184 (m), 1150 (m), 1121 (m), 1111 (s), 1063 (m), 1051 (m), 1027 (m), 1017 (s), 963 (m), 946 (m), 927 (w), 909 (m), 868 (m), 848 (m), 824 (s), 816 (s), 798 (s), 772 (s), 764 (s), 701 (m), 675 (m), 658 (m), 638 (w), 627 (w), 603 (m), 580 (m), 564 (m), 549 (m);

MS (EI, 70 eV) *m/z* (%): 410 (34), 409 ($[M]^+$, 100), 394 (14), 366 (14), 364 (20), 336 (12), 29 (31);

HRMS (EI): calcd. for $C_{28}H_{27}NO_2$ ($[M]^+$) 409.20363, found 409.20284.

Ethyl 4,7-di*p*-tolylquinoline-3-carboxylate (6g):



According to the general procedure compound **6g** was isolated by column chromatography as white crystals (123 mg, 87 %), mp = 118-119 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 2.43 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.16 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 7.21 (d, ^3J = 8.0 Hz, 2H, CH_{Ar}), 7.34 (d, ^3J = 3.2 Hz, 2H, CH_{Ar}), 7.34 (d, ^3J = 3.2 Hz, 2H, CH_{Ar}), 7.7 (d, ^3J = 7.9 Hz, 2H, CH_{Ar}), 7.7 (s, 1H, CH_{Ar}), 7.75 (dd, ^3J = 8.8 Hz, ^4J = 1.8 Hz, 1H, CH_{Ar}), 8.39 (d, ^4J = 1.9 Hz, 1H, CH_{Ar}), 9.35 (s, 1H, CH_{Ar});

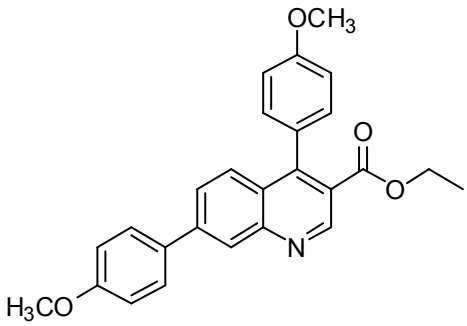
^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 21.3 (CH_3), 21.5 (CH_3), 61.35 (CH_2CH_3), 123.1 (C), 126.3, 126.55 (CH), 126.9 (CH), 127.5 (CH), 128.2 (CH), 128.9 (CH), 128.9 (CH), 130.0 (CH), 133.6 (C), 136.85 (C), 138.1 (C), 138.5 (C), 143.8 (C), 149.45 (C), 150.3 (C), 150.5 (CH), 166.7(C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3028 (w), 2989 (w), 2958 (w), 2918 (w), 2851 (w), 1911 (w), 1804 (w), 1731 (s), 1614 (m), 1578 (m), 1561 (m), 1513 (w), 1488 (m), 1441 (m), 1412 (w), 1379 (m), 1365 (m), 1349 (w), 1318 (w), 1289 (s), 1270 (m), 1258 (m), 1243 (w), 1222 (s), 1210 (s), 1183 (s), 1170 (s), 1155 (s), 1110 (s), 1025 (s), 1020 (s), 968 (w), 946 (m), 924 (m), 874 (w), 860 (w), 843 (s), 826 (s), 812 (s), 796 (s), 786 (s), 764 (s), 722 (s), 693 (s), 675 (s), 654 (m), 627 (w), 601 (s), 571 (m), 543 (s), 531 (m);

MS (GC, 70 eV) *m/z* (%): 382 (27), 381 ($[M]^+$, 100), 353 (12), 352 (16), 337 (15), 336 (52), 308 (18), 307 (11), 292 (11), 265 (11), 29 (31);

HRMS (EI): calcd. for $C_{26}H_{23}NO_2$ ($[M]^+$) 381.17233, found 381.17211.

Ethyl 4,7-bis(4-methoxyphenyl)quinoline-3-carboxylate (6h):



According to the general procedure compound **6h** was isolated by column chromatography as white crystals (132 mg, 86 %), mp = 120-121 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 3.88 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.18 (t, ^3J = 7.1 Hz, 2H, CH_2CH_3), 7.05 (dd, ^3J = 8.8 Hz, ^4J = 3.9 Hz, 4H, CH_{Ar}), 7.25 (d, ^3J = 8.7 Hz, 2H, CH_{Ar}), 7.64 – 7.8 (m, 4H, CH_{Ar}), 8.35 (d, ^4J = 1.2 Hz, 1H, CH_{Ar}), 9.32 (s, 1H, CH_{Ar});

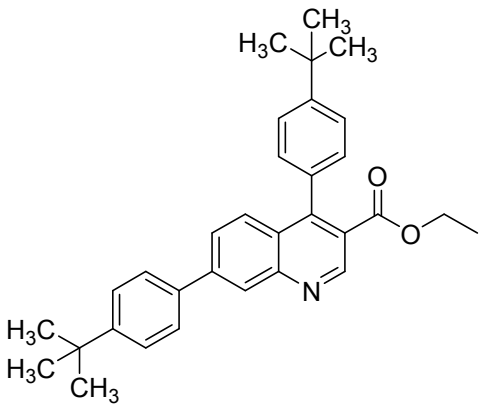
^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 55.3 (OCH_3), 55.4 (OCH_3), 61.2 (CH_2CH_3), 113.7 (CH), 114.7 (CH), 123.2, 126.0 (CH), 126.3 (C), 126.7 (CH), 128.1 (CH), 128.7 (CH), 128.8 (C), 130.3 (CH), 132.1 (C), 143.4 (C), 149.5 (C), 149.9 (C), 150.5 (CH), 159.8 (C), 160.2 (C), 166.8 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3102 (w), 3065 (w), 3041 (w), 2991 (w), 2955 (w), 2928 (w), 2897 (w), 2833 (w), 1895 (w), 1694 (s), 1608 (s), 1577 (m), 1510 (s), 1484 (m), 1458 (m), 1450 (m), 1440 (m), 1415 (m), 1401 (m), 1381 (m), 1368 (m), 1345 (m), 1328 (m), 1305 (m), 1285 (s), 1243 (s), 1176 (s), 1147 (s), 1109 (s), 1032 (s), 1022 (s), 971 (m), 944 (m), 926 (m), 896 (m), 871 (m), 847 (m), 832 (s), 825 (s), 800 (s), 765 (s), 730 (m), 700 (m), 676 (s), 660 (m), 632 (w), 621 (w), 600 (m), 582 (s), 558 (s), 545 (s), 527 (s);

MS (EI, 70 eV) *m/z* (%): 414 (28), 413 ($[M]^+$, 100), 368 (28);

HRMS (EI): calcd. for $C_{26}H_{23}NO_4$ ($[M]^+$) 413.16216, found 413.16092.

Ethyl 4,7-bis(4-tert-butylphenyl)quinoline-3-carboxylate (6i):



According to the general procedure compound **6i** was isolated by column chromatography as white crystals (136 mg, 86 %), mp = 205-206 ºC;

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.94 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 1.39 (s, 9H, $C(CH_3)_3$), 1.42 (s, 9H, $C(CH_3)_3$), 4.10 (q, ^3J = 7.2, 2H, CH_2CH_3), 7.26 (d, ^3J = 8.4 Hz, 2H, CH_{Ar}), 7.53 (d, ^3J = 8.4 Hz, 4H, CH_{Ar}), 7.72 (d, ^3J = 8.4 Hz, 2H,

CH_{Ar}), 7.73 (s, 1H, CH_{Ar}), 7.78 (dd, ^3J = 8.8 Hz, ^4J = 1.8 Hz, 1H, CH_{Ar}), 8.41 (d, ^4J = 1.7 Hz, 1H, CH_{Ar}), 9.34 (s, 1H, CH_{Ar}).

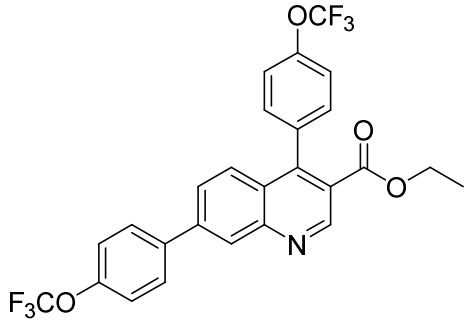
^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.7 (CH_2CH_3), 31.5 (C(CH_3)), 31.6 (C(CH_3)), 34.8, 34.9, 61.2 (CH_2CH_3), 123.4 (C), 125.1 (CH), 126.2 (CH), 126.3 (C), 126.6 (CH), 126.9 (CH), 127.3 (CH), 128.3 (CH), 128.8 (CH), 133.6 (C), 136.8 (C), 143.7 (C), 149.4 (C), 150.5 (2*C, C+CH), 151.4 (C), 151.7 (C), 167.0 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3036 (w), 2953 (m), 2902 (w), 2867 (w), 1913 (w), 1892 (w), 1799 (w), 1760 (w), 1702 (s), 1614 (m), 1572 (m), 1513 (w), 1486 (w), 1476 (w), 1461 (m), 1448 (m), 1403 (m), 1393 (m), 1365 (m), 1346 (w), 1322 (m), 1294 (m), 1271 (s), 1248 (m), 1224 (s), 1202 (m), 1194 (m), 1185 (m), 1152 (s), 1126 (s), 1113 (s), 1107 (s), 1017 (s), 993 (w), 963 (w), 944 (w), 929 (w), 907 (m), 879 (w), 866 (m), 849 (m), 829 (m), 822 (s), 815 (s), 798 (s), 765 (m), 753 (m), 742 (m), 676 (m), 658 (m), 638 (w), 625 (w), 598 (m), 563 (s), 551 (m), 540 (m);

HRMS (EI): calcd. for $C_{32}H_{35}NO_2$ ($[M]^+$) 465.26623, found 465.26571.

Ethyl 4,7-bis(4-(trifluoromethoxy)phenyl)quinoline-3-carboxylate (6j):

According to the general procedure compound **6j** was isolated by column chromatography as white crystals (131 mg, 68 %), mp = 119-120 ºC;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 4.15 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 7.31 – 7.42 (m, 6H, CH_{Ar}), 7.61 (d, ^3J = 8.7 Hz, 1H, CH_{Ar}), 7.71 – 7.80 (m, 3H, CH_{Ar}), 8.39 (d, ^4J = 1.8 Hz, 1H, CH_{Ar}), 9.41 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.7 (CH_2CH_3), 61.6 (CH_2CH_3), 120.6 (d, $^1J_{C\text{-}F}$ = 257.5 Hz), 120.7 (d, $^1J_{C\text{-}F}$ = 257.6 Hz, C), 120.8 (CH), 121.7 (CH), 123.3 (C), 126.3 (C), 127.0 (CH), 127.3 (CH), 128.1 (CH), 129.0 (CH), 130.5 (CH), 135.2 (C), 138.2 (C), 142.7 (C), 148.6 (C), 149.4 (C), 149.4 (d, $^3J_{C\text{-}F}$ = 1.9 Hz), 149.6 (d, $^3J_{C\text{-}F}$ = 2.0 Hz, C), 150.9 (CH), 166.2 (C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -57.78 (OCF_3), -57.77 (OCF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3036 (w), 2993 (w), 2960 (w), 2925 (w), 2825 (w), 1710. (s), 1617 (w), 1588 (w), 1571 (w), 1508 (m), 1486 (w), 1475 (w), 1450 (w), 1410 (w), 1400 (w), 1368 (m), 1346 (w), 1326 (w), 1294 (w), 1249 (s), 1219 (s), 1199 (s), 1159 (s), 1145 (s), 1102 (s), 1025 (s), 1016 (s), 958 (w), 946 (w), 917 (s), 854 (s), 834 (s),

792 (s), 768 (s), 740 (m), 698 (m), 676 (s), 634 (m), 624 (m), 611 (m), 583 (m), 533 (m);

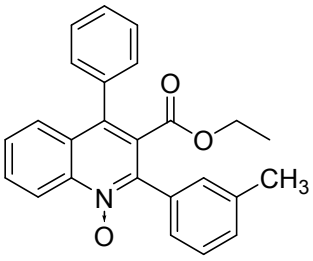
MS (EI, 70 eV) *m/z* (%): 522 (29), 521 (100), 493 (19), 477 (22), 476 (72), 448 (20), 362 (10), 351 (12), 69 (58), 29 (28);

HRMS (EI): calcd. for $C_{26}H_{17}F_6NO_4$ ($[M]^+$) 521.10563, found 521.10540.

General procedure for synthesis of compound 9:

To a toluene suspension (4 mL) of 3-(ethoxycarbonyl)-4-phenylquinoline 1-oxide (100 mg, 2 equiv.), 3-bromotoluene (30 mg, 1.1 equiv.), $Pd(OAc)_2$ (1.9 mg, 5 mol%), $PBu_2Me \cdot HBF_4$ (2.1 mg, 5 mol%) and K_2CO_3 (47 mg, 2.5 equiv.) were added under argon atmosphere. The reaction mixture was heated under argon atmosphere for 24 h at 110 °C. After cooling to 20 °C, the solution was diluted with water and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc).

3-(ethoxycarbonyl)-4-phenyl-2-(m-tolyl)quinoline 1-oxide (9):



According to the general procedure compound **9** was isolated as a light yellow semisolid (66 mg, 98 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.7 (t, ^3J = 7.1 Hz, 3H, CH_3), 2.4 (s, 3H, CH_3), 3.8 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 7.2 – 7.3 (m, 1H, CH_{Ar}), 7.4 – 7.5 (m, 6H), 7.5 – 7.5 (m, 3H), 7.6 (ddd, ^3J = 8.3 Hz, ^3J = 6.7 Hz, ^4J = 1.2 Hz, 1H, CH_{Ar}), 7.7 (ddd, ^3J = 8.5 Hz, ^4J = 1.6 Hz, ^5J = 0.6 Hz, 1H, CH_{Ar}), 7.8 (ddd, ^3J = 8.6 Hz, ^3J = 6.7 Hz, ^4J = 1.6 Hz, 1H, CH_{Ar}), 8.9 (dd, ^3J = 8.8 Hz, ^5J = 0.9 Hz, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4 (CH_2CH_3), 21.6 (CH_3), 61.7 (CH_2CH_3), 120.5 (CH), 126.6 (CH), 127.6 (CH), 128.5 (CH), 128.5 (CH), 128.7 (C), 128.9 (CH), 129.0 (CH), 129.9 (C), 130.0 (CH), 130.1 (CH), 130.5 (CH), 131.4 (CH), 131.8 (C), 134.8 (C), 135.6 (C), 138.1 (C), 141.9 (C), 143.5 (C), 165.6 (C=O);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3446 (w), 3055 (w), 3029 (w), 2954 (w), 2916 (w), 2848 (w), 2728 (w), 1933 (w), 1825 (w), 1730 (s), 1605 (w), 1587 (w), 1574 (w), 1542 (m), 1498 (w), 1484 (w), 1472 (w), 1461 (m), 1441 (m), 1364 (m), 1326 (s), 1296 (s), 1223

(s), 1213 (s), 1178 (s), 1136 (m), 1124 (m), 1094 (s), 1081 (s), 1035 (s), 1020 (s), 1000 (w), 984 (w), 967 (w), 938 (w), 898 (w), 882 (w), 856 (w), 848 (w), 812 (w), 775 (s), 763 (s), 742 (s), 730 (s), 711 (s), 701 (s), 692 (s), 667 (s), 638 (m), 617 (w), 604 (s), 588 (s), 568 (m), 546 (m), 528 (m);

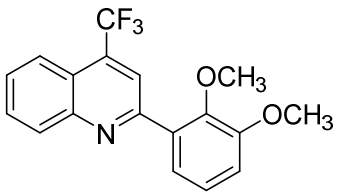
MS (GC, 70 eV) *m/z* (%): 383 (41), 382 (62), 367 (14), 354 (240, 339 (29), 338 (100), 336 (14), 322 (28), 310 (17), 308 (10), 294 (23), 292 (11), 291 (12), 283 (12), 282 (20), 280 (13), 278 (16), 277 (12), 20 (11), 176 (11), 29 (46);

HRMS (EI): calcd. for $C_{25}H_{21}NO_3$ ($[M]^+$) 383,15214, found 383,15307.

General procedure for synthesis of compounds 10a-n:

In a pressure tube or Schlenk flask corresponding 2-chloro-4-(trifluoromethyl)quinoline **9** (1 equiv.), arylboronic acid (1.1-1.5 equiv.), $Pd(PPh_3)_4$ (3 mol %) and anhydrous potassium carbonate (2 equiv.) in 5 mL extra dry dimethylformamide were added under argon atmosphere. The reaction mixture was stirred at 130 °C for about 12 h. The solvent was evaporated under reduced pressure and residue was purified by column chromatography (silica gel, heptane/ethyl acetate).

2-(2,3-dimethoxyphenyl)-4-(trifluoromethyl)quinoline (10a):



Starting from 2-chloro-4-(trifluoromethyl)quinoline (100 mg, 0.43 mmol), 2,3-dimethoxyphenylboronic acid (94.3 mg, 0.52 mmol), potassium carbonate (96 mg, 0.69 mmol) and $Pd(PPh_3)_4$ (15 mg, 0.01 mmol), the product **10a** was isolated as a white solid (136 mg, 95 %); mp = 85 – 87 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.75 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 7.07 (dd, ^3J = 8.2 Hz, ^4J = 1.6 Hz, 1H, CH_{Ar}), 7.23 (t, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.50 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.68 (ddd, ^3J = 8.4 Hz, ^3J = 6.9 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.81 (ddd, ^3J = 8.4 Hz, ^3J = 6.9 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 8.17 (dt, ^3J = 8.5 Hz, ^4J = 2.0 Hz, 1H, CH_{Ar}), 8.27 (dd, ^3J = 8.5 Hz, ^4J = 0.6 Hz, 1H, CH_{Ar}), 8.30 (s, 1H, CH_{Ar}).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.2 (OCH_3), 61.4 (OCH_3), 114.0 (CH), 120.5 (q, $^3J_{C\text{-}F}$ = 5.5 Hz, CH), 122.0 (C), 122.9 (CH), 123.8 (d, $^1J_{C\text{-}F}$ = 274.9 Hz, C), 124.0 (q, $^3J_{C\text{-}F}$ = 2.3 Hz, CH), 124.8 (CH), 128.1 (CH), 130.1 (CH), 130.8 (CH), 133.8 (C), 133.9 (q, $^2J_{C\text{-}F}$ = 31.6 Hz), 147.8 (C), 149.1 (C), 153.3 (C), 156.4 (C);

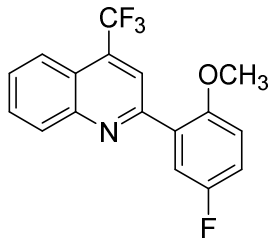
^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.43 (CF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3069 (w), 3007 (w), 2964 (m), 2937 (w), 2840 (w), 1555 (m), 1476 (s), 1371 (s), 1371 (s), 1262 (s), 1132 (s), 999 (s), 764 (s), 683 (s), 593 (m).

MS (GC-MS) *m/z* (%): 334 ($[M+H]^+$, 19), 333 ($[M]^+$, 100), 332 (39), 318 (49), 314 (18), 304 (37), 302 (33), 290 (39), 287 (27), 274 (16), 273 (23), 272 (37), 264 (26), 261 (12), 247 (14), 246 (40), 221 (10), 204 (22), 198 (65), 196 (12), 191 (14), 178 (15), 176 (22), 159 (18).

HRMS (EI): calcd for $C_{18}F_3H_{14}NO_2$ ($[M]^+$) 333.09711 found 333.09671.

2-(5-fluoro-2-methoxyphenyl)-4-(trifluoromethyl)quinoline (10b):



Starting from 2-chloro-4-(trifluoromethyl)quinoline (100 mg, 0.43 mmol), 5-fluoro-2-methoxyphenylboronic acid (150 mg, 0.65 mmol), potassium carbonate (144 mg, 1.04 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), the product **10b** was isolated as a white solid (153 mg, 73 %); mp = 105 – 107 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.89 (s, 3H, OCH_3), 6.99 (dd, ^3J = 9.1 Hz, ^3J = 4.3 Hz, 1H, CH_{Ar}), 7.15 (ddd, ^3J = 9.0 Hz, ^3J = 7.6 Hz, ^4J = 3.2 Hz, 1H, CH_{Ar}), 7.69 (ddd, ^3J = 8.4 Hz, ^3J = 6.9 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 7.73 (dd, ^3J = 9.1 Hz, ^3J = 3.2 Hz, 1H, CH_{Ar}), 7.81 (ddd, ^3J = 8.4 Hz, ^3J = 6.9 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 8.16 (dt, ^3J = 8.6 Hz, ^4J = 2.1 Hz, 1H, CH_{Ar}), 8.26 (ddd, ^3J = 8.5 Hz, ^4J = 1.2 Hz, ^5J = 0.5 Hz, 1H, CH_{Ar}), 8.32 (s, 1H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 56.4 (OCH_3), 112.9 (d, $^3J_{C-F}$ = 8.0 Hz, CH), 117.3 (d, $^2J_{C-F}$ = 23.2 Hz, CH), 118.0 (d, $^2J_{C-F}$ = 24.5 Hz, CH), 120.4 (q, $^4J_{C-F}$ = 5.6 Hz, CH), 122.0 (C), 123.8 (d, $^1J_{C-F}$ = 274.6 Hz, CH), 123.9 (q, $^4J_{C-F}$ = 2.1 Hz), 128.2 (CH), 129.5 (d, $^3J_{C-F}$ = 7.4 Hz), 130.2 (CH), 130.7 (CH), 133.7 (q, $^2J_{C-F}$ = 31.5 Hz, C), 149.1, 153.8 (d,$^4J_{C-F}$ = 2.1 Hz, C),155.2 (d, $^4J_{C-F}$ = 2.0 Hz, C), 157.6 (d, $^1J_{C-F}$ = 239.4 Hz, C).

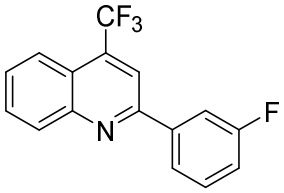
^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.51 (CF_3), -112.18 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3080 (w), 3017 (w), 2929 (w), 2840 (w), 1610 (w), 1493 (s), 1431 (m), 1352 (m), 1251 (s), 1166 (s), 1117 (s), 1032 (m), 881 (m), 809 (m), 751 (s), 692 (m), 643 (m), 545 (w).

MS (GC-MS) *m/z* (%): 322 ($[M+H]^+$, 16), 321 ($[M]^+$, 86), 320 (50), 292 (38), 291 (24), 290 (31), 252 (34), 237 (11), 223 (10), 222 (59), 221 (12), 208 (19), 199 (12), 198 (100), 176 (12).

HRMS (EI): calcd for $C_{17}F_4H_{11}NO$ ($[M]^+$) 321.07713, found 321.07666.

2-(3-fluorophenyl)-4-(trifluoromethyl)quinoline (10c):



Starting from 2-chloro-4-(trifluoromethyl)quinoline (100 mg, 0.43 mmol), 3-fluorophenylboronic acid (73 mg, 0.52 mmol), potassium carbonate (196 mg, 0.69 mmol) and $Pd(PPh_3)_4$ (3 mol %, 15 mg, 0.01 mmol), the product **10c** was isolated as a white solid (115 mg, 92 %); mp = 67 – 69 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (tdd, ^3J = 8.3 Hz,^4J = 2.6 Hz, ^4J = 1.0 Hz, 1H, CH_{Ar}), 7.48-7.58 (m, 1H, CH_{Ar}), 7.69 (ddd, ^3J = 8.5 Hz, ^4J = 7.4 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 7.85 (ddd, ^3J = 8.5 Hz, ^3J = 7.0 Hz, ^4J = 1.32 Hz, 1H, CH_{Ar}), 7.91-8.02 (m, 2H, CH_{Ar}), 8.09-8.20 (m, 2H, CH_{Ar}), 8.28 (ddd, ^3J = 8.5 Hz, ^4J = 1.4 Hz, ^4J = 0.7 Hz, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 114.6 (d, $^2J_{C\text{-}F}$ = 23.0 Hz, CH), 115.9 (q, $^4J_{C\text{-}F}$ = 5.4 Hz), 117.1 (d, $^2J_{C\text{-}F}$ = 21.4 Hz, CH), 122.2 (q, $^4J_{C\text{-}F}$ = 0.9 Hz), 123.2 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, CH), 123.6 (d, $^1J_{C\text{-}F}$ = 274.8 Hz), 124.0 (q, $^4J_{C\text{-}F}$ = 2.1 Hz, CH), 128.4 (CH), 130.6 (CH), 130.7 (CH), 130.8 (CH), 135.4 (q, $^2J_{C\text{-}F}$ = 31.6 Hz, C), 140.8 (d, $^3J_{C\text{-}F}$ = 7.6 Hz, C), 149.1 (C), 155.3 (d, $^4J_{C\text{-}F}$ = 2.8 Hz, C), 163.6 (d, $^1J_{C\text{-}F}$ = 246.4 Hz, C).

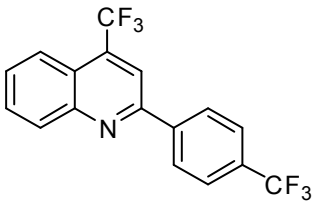
^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.48 (CF_3), -112.16 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3086 (w), 3053 (w), 2956 (w), 2924 (m), 2853 (w), 1933 (w), 1853 (w), 1776 (w), 1613 (m), 1449 (s), 1356 (s), 1253 (s), 1115 (br, vs), 880 (s), 762 (vs), 693 (m), 617 (m).

MS (GC-MS) *m/z* (%): 292 ($[M+H]^+$, 17), 291 ($[M]^+$,100), 290 (29), 222 (50), 221(11);

HRMS (EI): calcd for $C_{16}F_4H_9N_1$ ($[M]^+$) 291.06656, found 291.06612.

4-(trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)quinoline (10d):



Starting from 2-chloro-4-(trifluoromethyl)quinoline (100 mg, 0.43 mmol), 4-(trifluoromethyl)phenylboronic acid (99 mg, 0.52 mmol), potassium carbonate (196 mg, 0.69 mmol) and $Pd(PPh_3)_4$ (15 mg, 0.01 mmol), the product **10d** was isolated as a white solid (61 mg, 41.5 %); mp = 81 – 83 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (ddd, ^3J = 8.5 Hz, ^3J = 7.0 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.79-7.90 (m, 3H, CH_{Ar}), 8.14-8.22 (m, 2H, CH_{Ar}), 8.28-8.36 (m, 3H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.9 (q, $^3J_{C\text{-}F}$ = 5.4 Hz, CH), 122.3 (d, $^4J_{C\text{-}F}$ = 1.2 Hz), 123.6 (d, $^1J_{C\text{-}F}$ = 275.0 Hz), 124.1 (d, $^4J_{C\text{-}F}$ = 2.4 Hz, CH), 124.2 (d, $^1J_{C\text{-}F}$ = 275.0 Hz), 126.1 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, CH), 128.0 (CH), 128.7 (CH), 130.9 (CH), 130.9 (CH), 132.0 (q, $^2J_{C\text{-}F}$ = 32.7 Hz), 135.6 (q, $^2J_{C\text{-}F}$ = 31.8 Hz), 141.7 (C), 149.2 (C), 155.1 (C);

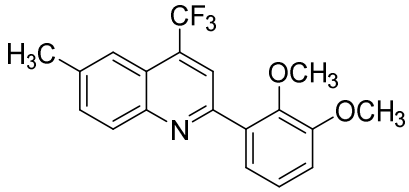
^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.46 (CF_3), -62.71 (CF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3101 (w), 3060 (w), 2961 (w), 2928 (w), 2852 (w), 1614 (m), 1408 (m), 1322 (s), 1109 (vs), 1016 (s), 841 (s), 766 (s), 595 (m).

MS (GC-MS) *m/z* (%): 342([M+H]$^+$, 19), 341 ([M]$^+$ 100), 340 (21), 322 (12), 273 (11), 272 (59), 252 (11).

HRMS (EI): calcd for $C_{17}F_6H_9N$ ([M]$^+$) 341.06337, found 341.06319.

2-(2,3-dimethoxyphenyl)-6-methyl-4-(trifluoromethyl)quinoline (10e):



Starting from 2-chloro-6-methyl-4-(trifluoromethyl)quinoline (100 mg, 0.41 mmol), 2,3-dimethoxyphenylboronic acid (89 mg, 0.49 mmol), potassium carbonate (109 mg, 0.78 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), the product **10e** was isolated as a white solid (128 mg, 85.5 %); mp = 99 – 101 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 7.06 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.23 (t, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.50 (dd, ^3J = 7.7 Hz, ^3J = 1.5 Hz, 1H, CH_{Ar}), 7.65 (dd, ^3J = 8.6 Hz, ^4J = 1.8 Hz, 1H, CH_{Ar}), 7.92 (br. s., 1H, CH_{Ar}), 8.18 (d, ^3J = 8.7 Hz, 1H, CH_{Ar}), 8.28 (s, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2(CH_3), 56.2 (OCH_3), 61.4 (OCH_3), 113.8 (CH), 120.4 (d, $^3J_{C\text{-}F}$ = 5.6 Hz, CH), 122.0 (C), 122.8 (CH), 122.9 (d, $^4J_{C\text{-}F}$ = 2.1 Hz, CH), 123.9 (d, $^1J_{C\text{-}F}$ = 274.7 Hz, C), 124.8 (CH), 130.3 (CH), 132.4 (CH), 133.2 (q, $^2J_{C\text{-}F}$ = 31.3 Hz, C), 133.7 (C), 138.4 (C), 147.6 (C), 147.7 (C), 153.3 (C), 155.3(C);

^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.49 (CF_3);

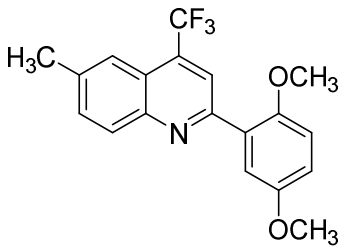
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3088 (w), 3005 (w), 2973 (w), 2933 (m), 2868 (w), 2833 (m), 1554 (m), 1469 (m), 1371 (s), 1264 (s), 1142 (s), 1113 (s), 1005 (s), 830 (m), 739 (s), 680 (s), 572 (w).

MS (GC-MS) *m/z* (%): 348 ([M]$^+$, 20), 347 ([M]$^+$ 100), 346 (37), 332 (49), 328 (15), 318 (33), 304 (35), 301 (28), 288 (15), 287 (21), 286 (26), 278 (21), 260 (18),

246 (13), 212 (70), 190 (11), 166 (18).

HRMS (EI): calcd for $C_{19}F_3H_{16}NO_2$ ($[M]^+$) 347.11276, found 347.11223.

2-(2,5-dimethoxyphenyl)-6-methyl-4-(trifluoromethyl)quinoline (10f):



Starting from 2-chloro-6-methyl-4-(trifluoromethyl)quinoline (100 mg, 0.41 mmol), 2,5-dimethoxyphenylboronic acid (73 mg, 0.52 mmol), potassium carbonate (109 mg, 0.78 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), the product **10f** was isolated as a yellow solid (135 mg, 95 %); mp = 71 – 73 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.60 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 6.98 – 7.00 (m, 2H, CH_{Ar}), 7.52 (dd, ^4J = 2.1 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.63 (dd, ^3J = 8.7 Hz, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.9 (s, 1H, CH_{Ar}), 8.15 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 8.26 (s, 1H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 22.2 (CH_3), 56.0 (OCH_3), 56.5 (OCH_3), 113.3 (CH), 116.2 (CH), 116.8 (CH), 120.6 (q, $^3J_{C\text{-}F}$ = 5.7 Hz, CH), 122.0 (d, $^4J_{C\text{-}F}$ = 1.0 Hz), 122.8 (d, $^4J_{C\text{-}F}$ = 2.3 Hz, CH), 124.0 (d, $^1J_{C\text{-}F}$ = 274.6 Hz), 129.1 (C), 130.3 (CH), 132.3 (CH), 132.8 (d, $^2J_{C\text{-}F}$ = 31.2 Hz, C), 138.1 (C), 147.8 (C), 151.8 (C), 154.3 (C), 155.3 (C);

^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.45 (CF_3);

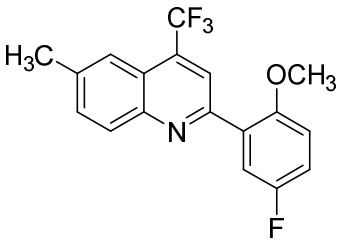
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3150 (w), 3014 (w), 2956 (w), 2840 (w), 1609 (w), 1501 (s), 1415 (m), 1350 (s), 1255 (s), 1209 (s), 1139 (s), 1113 (s), 1038 (s), 916 (m), 879 (m), 806 (m), 687 (m), 648 (m), 540 (w).

MS (GC-MS) *m/z* (%): 348 ($[M+H]^+$, 20), 347 ($[M]^+$ 90), 346 (46), 332 (15), 318 (34), 317 (13), 316 (27), 289 (11), 288 (11), 287 (15), 286 (16),278 (31), 261 (13), 260 (22), 246 (11), 213 (15), 212 (100).

HRMS (EI): calcd for $C_{19}F_3H_{16}NO_2$ ($[M]^+$) 347.11276, found 347.11221.

2-(5-fluoro-2-methoxyphenyl)-6-methyl-4-(trifluoromethyl)quinoline (10g):

Starting from 2-chloro-6-methyl-4-(trifluoromethyl)quinoline (100 mg, 0.41 mmol), 5-fluoro-2-methoxyphenylboronic acid (83 mg, 0.49 mmol), potassium carbonate (109 mg, 0.78 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), the product **10g** was isolated as a white solid (134 mg, 97 %); mp = 103 – 105 °C.



^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 6.99 (dd, ^{3}J = 9.0 Hz, ^{3}J = 4.3 Hz, 1H, CH_{Ar}), 7.14 (ddd, ^{3}J = 9.0 Hz, ^{3}J = 7.7 Hz, ^{4}J = 3.0 Hz, 1H, CH_{Ar}), 7.65 (dd, ^{3}J = 8.7 Hz, ^{4}J = 1. 9 Hz, 1H, CH_{Ar}), 7.73 (dd, ^{3}J = 9.0 Hz, ^{3}J = 3.2 Hz, 1H, CH_{Ar}), 7.91 (br. s., 1H, CH_{Ar}), 8.16 (d, ^{3}J = 8.7 Hz, 1H, CH_{Ar}), 8.29 (s, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3 (CH_3), 56.4 (OCH_3), 112.9 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz, CH), 117.1 (d, $^{2}J_{C\text{-}F}$ = 23.1 Hz, CH), 118.0 (d, $^{2}J_{C\text{-}F}$ = 24.5 Hz, CH), 120.3 (q, $^{3}J_{C\text{-}F}$ = 5.7 Hz, CH), 122.1 (C), 122.8 (q, $^{4}J_{C\text{-}F}$ = 2.0 Hz, CH), 123.9 (d, $^{1}J_{C\text{-}F}$ = 274.6 Hz, C), 129.5 (d, $^{3}J_{C\text{-}F}$ = 7.3 Hz, C), 130.3 (CH), 132.5 (CH), 133.0 (q, $^{2}J_{C\text{-}F}$ = 31.3 Hz, C), 138.5, 147.7 (C), 153.7 (d, $^{4}J_{C\text{-}F}$ = 2.1 Hz, C), 154.1 (d, $^{4}J_{C\text{-}F}$ = 1.9 Hz, C), 157.6 (d, $^{1}J_{C\text{-}F}$ = 239.3 Hz, C).

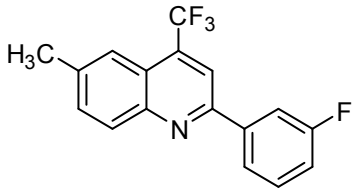
^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.50 (CF_3), -123.21 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3145 (w), 3085 (w), 3022 (w), 2965 (w), 2921 (m), 2841 (w), 1825 (w), 1603 (m), 1496 (m), 1348 (s), 1348 (s), 1250 (s), 1112 (vs), 1019 (s), 901 (s), 824 (m), 799 (m), 742 (m), 690 (m), 657 (m), 539 (m).

MS (GC-MS) *m/z* (%): 336 ($[M+H]^+$,14), 335 ($[M]^+$ 76), 334 (43), 306 (33), 305 (33), 304 (22), 266 (26), 236 (20), 213 (13), 212 (100);

HRMS (EI): calcd for $C_{18}F_4H_{13}NO$ ($[M]^+$) 335.09278, found 335.09228.

2-(3-fluorophenyl)-6-methyl-4-(trifluoromethyl)quinoline (10h):



Starting from 2-chloro-6-methyl-4-(trifluoromethyl)quinoline (100 mg, 0.41 mmol), 3-fluorophenylboronic acid (69 mg, 0.49 mmol), potassium carbonate (109 mg, 0.78 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), the product **10h** was isolated as a white solid (117 mg, 93.7 %); mp = 126 – 128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61 (s, 3H, CH_3), 7.19 (tdd, ^{3}J = 8.3 Hz, ^{4}J = 2.6 Hz, ^{4}J = 0.9 Hz, 1H, CH_{Ar}), 7.46-7.56 (m, 1H, CH_{Ar}), 7.63-7.70 (m, 1H, CH_{Ar}), 7.87-7.99 (m, 3H, CH_{Ar}), 8.10 (s, 1H, CH_{Ar}), 8.15 (d, ^{3}J = 8.7 Hz, 1H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 22.3 (CH_3), 114.5 (d, $^{2}J_{C\text{-}F}$ = 23.0 Hz, CH), 115.8 (q, $^{3}J_{C\text{-}F}$ = 5.4 Hz, CH), 116.9 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz, CH), 122.2 (d, $^{4}J_{C\text{-}F}$ = 1.3 Hz, C), 122.9 (q, $^{4}J_{C\text{-}F}$ = 2.2 Hz, CH), 123.0 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz, CH), 123.7 (d, $^{1}J_{C\text{-}F}$ = 274.7 Hz, C), 130.5 (CH), 130.6 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz, CH), 133.0 (CH), 134.6 (d, $^{2}J_{C\text{-}F}$ = 31.6 Hz, C), 138.7, 140.9 (d, $^{3}J_{C\text{-}F}$ = 7.6 Hz, C), 147.8, 154.3 (d, $^{4}J_{C\text{-}F}$ = 2.7 Hz,

C), 163.6 (d, $^{1}J_{C\text{-}F}$ = 246.2 Hz, C).

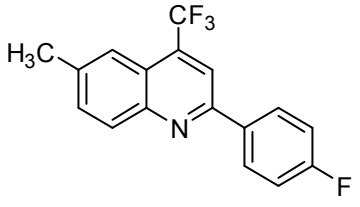
^{19}F NMR (300 MHz, $CDCl_3$): δ = -112.29 (CF), -61.54 (CF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3080 (w), 2961 (w), 2923 (w), 2855 (w), 1611 (m), 1594 (m), 1448 (m), 1354 (s), 1257 (s), 1187 (m), 1146 (s), 1114 (s), 878 (s), 777 (s), 688 (m), 579 (w).

MS (GC-MS) *m/z* (%): 306 ($[M+H]^+$, 19), 305 ($[M]^+$, 100), 304 (22), 236 (22);

HRMS (EI): calcd for $C_{17}NF_4H_{11}$ ($[M]^+$) 305.08221, found 305.08228.

2-(4-fluorophenyl)-6-methyl-4-(trifluoromethyl)quinoline (10i):



Starting from 2-chloro-6-methyl-4-(trifluoromethyl)quinoline (100 mg, 0.41 mmol), 4-fluorophenylboronic acid (73 mg, 0.52 mmol), potassium carbonate (109 mg, 0.78 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), the product **10i** was isolated as a yellow solid (111 mg, 95 %); mp = 130 – 132 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.61 (s, 3H, CH_3), 7.23 (*pseudo* t, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.62-7.69 (m, 1H, CH_{Ar}), 7.89 (br. s., 1H, CH_{Ar}), 7.98-8.23 (m, 4H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 22.2 (CH_3), 115.7 (q, $^{3}J_{C\text{-}F}$ = 5.5 Hz, CH), 116.1 (d, $^{2}J_{C\text{-}F}$ = 22.0 Hz, CH), 121.9 (d, $^{3}J_{C\text{-}F}$ = 1.4 Hz, C), 122.9 (q, $^{4}J_{C\text{-}F}$ = 2.3 Hz, CH), 123.8 (q, $^{1}J_{C\text{-}F}$ = 274.2 Hz, C), 129.4 (d, $^{3}J_{C\text{-}F}$ = 8.7 Hz, CH), 130.3 (CH), 132.9 (CH), 134.5 (d, ^{2}J = 31.3 Hz, C), 134.8 (q, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 138.4 (C), 147.9 (C), 154.7 (C), 164.2 (d, $^{1}J_{C\text{-}F}$ = 249.9 Hz, C).

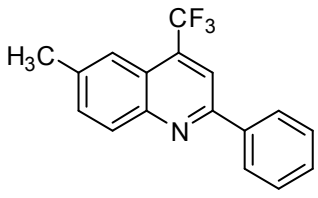
^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.49 (CF_3), -112.0 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3061 (w), 2974 (w), 2959 (w), 2924 (m), 2859 (w) 1601 (m), 1357 (s), 1321 (s), 1114 (s), 884 (m), 837 (s), 682 (m), 585 (m).

MS (GC-MS) *m/z* (%): 306 ($[M+H]^+$, 18), 305 ($[M]^+$, 100), 304 (23), 236 (21).

HRMS (EI): calcd for $C_{17}F_4NH_{11}$ ($[M]^+$) 305.08221, found 305.08206.

6-methyl-2-phenyl-4-(trifluoromethyl)quinoline (10j):



Starting from 2-chloro-6-methyl-4-(trifluoromethyl)quinoline (100 mg, 0.41 mmol), phenylboronic acid (60 mg, 0.49 mmol), potassium carbonate (109 mg, 0.78 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), the product **10j** was isolated as a yellow solid (110 mg, 94 %); mp = 100 – 102 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3H, CH_3), 7.46-7.61 (m, 3H, CH_{Ar}),

7.66 (dd, ^{3}J = 8.7 Hz, 1H, CH_{Ar}), 7.84-7.94 (m, 1H, CH_{Ar}), 8.11-8.23 (m, 4H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2 (CH_3), 116.1 (q, $^{3}J_{C\text{-}F}$ = 5.5 Hz, CH), 122.0 (q, $^{3}J_{C\text{-}F}$ = 1.5 Hz, C), 122.9 (q, $^{4}J_{C\text{-}F}$ = 2.2 Hz, CH), 123.8 (q, $^{1}J_{C\text{-}F}$ = 275.1 Hz), 127.5 (CH), 129.1 (CH), 130.0 (CH), 130.4 (CH), 132.8 (CH), 134.4 (q, $^{2}J_{C\text{-}F}$ = 31.4 Hz, C), 138.3 (C), 138.7 (C), 147.9 (C), 155.8 (C);

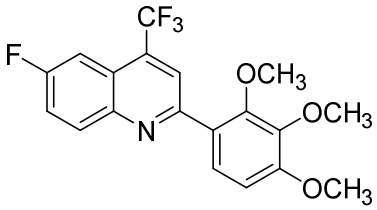
^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.45 (CF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068 (w), 3034 (w), 2979 (w), 2960 (w), 2924 (w), 2858 (w), 2222 (m), 1966 (w), 1794 (w), 1700 (w), 1604 (m), 1494 (m), 1373 (s), 1259 (s), 1146 (s), 1115 (s), 897 (s), 830 (m), 753 (s), 683 (s), 583 (m).

MS (GC-MS) *m/z* (%): 288 ([M+H]$^{+}$, 18), 287 ([M]$^{+}$, 100), 286 (25), 218 (22).

HRMS (EI): calcd for $C_{17}F_3NH_{12}$ ([M]$^{+}$) 287.09147, found 287.09124.

6-fluoro-4-(trifluoromethyl)-2-(2,3,4-trimethoxyphenyl)quinoline (10k):



Starting from 2-chloro-6-fluoro-4-(trifluoromethyl)-quinoline (100 mg, 0.40 mmol), 2,3,4-trimethoxyphenyl-boronic acid (102 mg, 0.48 mmol), potassium carbonate (106 mg, 0.77 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), the product **10k** was isolated as a brown solid (132 mg, 87 %); mp = 87 – 89 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.87 (d, ^{3}J = 8.8 Hz, 1H, CH_{Ar}), 7.57 (ddd, ^{3}J = 9.3 Hz, ^{3}J = 8.0 Hz, ^{4}J = 2.7 Hz, 1H, CH_{Ar}), 7.69 (d, ^{3}J = 8.83 Hz, 1H, CH_{Ar}), 7.72-7.81 (m, 1H, CH_{Ar}), 8.24 (ddd, ^{3}J = 9.1 Hz, ^{3}J = 5.5 Hz, ^{4}J = 0.5 Hz, 1H, CH_{Ar}), 8.32 (s, 1H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 56.3 (OCH_3), 61.2 (OCH_3), 61.6 (OCH_3), 108.1 (dq, $^{2}J_{C\text{-}F}$ = 24.5 Hz, $^{4}J_{C\text{-}F}$ = 2.3 Hz, CH), 108.2 (CH), 120.4 (d, $^{2}J_{C\text{-}F}$ = 25.6 Hz, CH), 121.0 (d, $^{4}J_{C\text{-}F}$ = 5.5 Hz, CH), 122.5 (dd, $^{3}J_{C\text{-}F}$ = 10.5 Hz, $^{3}J_{C\text{-}F}$ = 1.0 Hz, C), 123.6 (d, $^{1}J_{C\text{-}F}$ = 274.3 Hz), 125.8 (CH), 125.9 (C), 133.0 (d, $^{3}J_{C\text{-}F}$ = 9.4 Hz, CH), 133.6 (dd, $^{2}J_{C\text{-}F}$ = 31.7 Hz, $^{4}J_{C\text{-}F}$ = 5.6 Hz, C), 142.6 (C), 146.3 (d, $^{4}J_{C\text{-}F}$ = 0.5 Hz), 152.6, 155.4 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz), 155.5 (C), 161.2 (d, $^{1}J_{C\text{-}F}$ = 250.0 Hz, C).

^{19}F NMR (300 MHz, $CDCl_3$): δ = -110.21 (CF), -62.07 (CF_3);

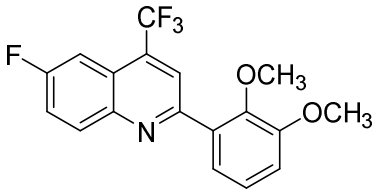
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3165 (w), 3111 (w), 3074 (w), 3000 (w), 2967 (m), 2939 (m), 2840 (w), 1593 (m), 1454 (m), 1357 (m), 1268 (m), 1163 (m), 1085 (s), 1019 (s), 868 (m), 803 (m), 679 (m), 617 (w).

MS (GC-MS) *m/z* (%): 382 ([M+H]$^{+}$, 18), 381 ([M]$^{+}$ 86), 380 (28), 367 (20), 366

(100), 362 (14), 352 (12), 350 (16), 348 (10), 338 (21), 336 (20), 335 (35), 323 (42), 320 (20), 312 (15), 308 (20), 294 (10), 280 (26), 267 (11), 266 (36), 265 (10), 264 (11), 253 (10), 252 (48), 216 (17), 194 (13), 183 (19), 182 (11);

HRMS (EI): calcd for $C_{19}F_4NH_{15}O_3$ ($[M]^+$) 381.09826, found 381.09796.

2-(2,3-dimethoxyphenyl)-6-fluoro-4-(trifluoromethyl)quinoline (10l):



Starting from 2-chloro-6-fluoro-4-(trifluoromethyl)quinoline (100 mg, 0.40 mmol), 2,3-dimethoxyphenylboronic acid (102 mg, 0.48 mmol), potassium carbonate (106 mg, 0.77 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), the product **10l** was isolated as a white solid (124 mg, 88.9 %); mp = 96 – 99 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.76 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 7.08 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.24 (t, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.50 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, CH_{Ar}), 7.59 (ddd, ^3J = 9.2 Hz, ^3J = 8.0 Hz, ^3J = 2.7 Hz, 1H, CH_{Ar}), 7.75-7.83 (m, 1H, CH_{Ar}), 8.29 (dd, ^3J = 9.2 Hz, ^3J = 5.5 Hz, 1H, CH_{Ar}), 8.34 (s, 1H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 56.2 (OCH_3), 61.4 (OCH_3), 108.1 (dq, $^2J_{C\text{-}F}$ = 24.7, $^4J_{C\text{-}F}$ = 2.3 Hz, CH), 114.1 (CH), 120.5 (d, $^2J_{C\text{-}F}$ = 25.6 Hz, CH), 121.3 (q, $^3J_{C\text{-}F}$ = 5.4 Hz, CH), 122.7 (CH), 124.8 (CH), 125.8 (q, $^1J_{C\text{-}F}$ = 274.2 Hz, C), 133.2 (d, $^3J_{C\text{-}F}$ = 9.2 Hz, CH), 133.3 (C), 133.7 (dd, J = 31.8, 5.8 Hz, C), 146.2 (C), 147.7 (C), 153.3 (C), 155.7 (d,$^4J_{C\text{-}F}$ = 2.7 Hz, C), 161.4 (d, $^1J_{C\text{-}F}$ = 249.9 Hz, C).

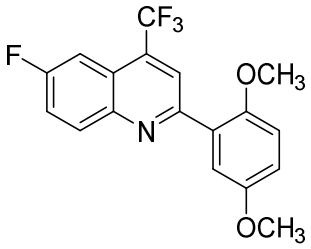
^{19}F NMR (300 MHz, $CDCl_3$): δ = -62.09 (CF_3), -109.72 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3077 (w), 3019 (w), 2962 (w), 2938 (w); 2866 (w), 2839 (w), 1628 (w), 1558 (m), 1473 (m), 1375 (m); 1273 (s), 1273 (br. s), 1127 (br. s), 1049 (s), 1004 (s), 325 (m), 792 (m); 753 (s), 682 (m), 626 (w).

MS (GC-MS) *m/z* (%): 352 ($[M]^+$, 19), 351 ($[M]^+$, 100) , 350 (41), 336 (37), 332 (18), 322 (36), 320 (30), 308 (39), 305 (25), 292 (17), 291 (19), 290 (30), 282 (23), 279 (10), 265 (13), 264 (38), 239 (12), 222 (16), 216 (59), 196 (12), 194 (16), 168 (15).

HRMS (EI): calcd for $C_{18}F_4H_{13}NO_{24}$ ($[M]^+$) 351.08769, found 351.08750.

2-(2,5-dimethoxyphenyl)-6-fluoro-4-(trifluoromethyl)quinoline (10m):



Starting from (100 mg, 0.43 mmol), 2,5-dimethoxyphenylboronic acid (87 mg, 0.48 mmol), potassium carbonate (106 mg, 0.77 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), the product **10m** was isolated as a yellow solid (127 mg, 92 %); mp = 82 – 84 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 7.00-7.04 (m, 2H), 7.51-7.63 (m, 2H, CH_{Ar}), 7.73-7.81 (m, 1H, CH_{Ar}), 8.27 (dd, ^3J = 9.2 Hz, ^3J = 5.60 Hz, 1H, CH_{Ar}), 8.35 (s, 1H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 56.0 (OCH_3), 56.5 (OCH_3), 108.1 (dq, $^2J_{C-F}$ = 24.3, $^4J_{C-F}$ = 2.3 Hz, CH), 113.2 (CH), 116.2 (CH), 117.0 (CH), 120.4 (d, $^2J_{C-F}$ = 25.6 Hz, CH), 121.5 (q, $^3J_{C-F}$ = 5.5 Hz, CH), 122.7 (d, J = 10.8 Hz, C), 123.6 (q, $^2J_{C-F}$ = 274.5 Hz, C), 128.6 (C), 133.2 (d, $^3J_{C-F}$ = 9.2 Hz, CH), 133.2 (dd, $^2J_{C-F}$ = 31.6 Hz, $^4J_{C-F}$ = 5.9 Hz, C), 146.3 (d, J = 0.9 Hz, C), 151.8 (C), 154.3 (C), 155.6 (d, $^4J_{C-F}$ = 3.2 Hz, C), 161.3 (d, $^1J_{C-F}$ = 250.0 Hz, C).

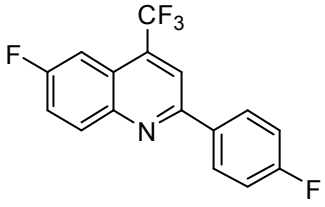
^{19}F NMR (300 MHz, $CDCl_3$): δ = -62.07 (CF_3), -109.97 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3073 (w), 3049 (w), 2948 (w), 2842 (w), 1626 (w), 1499 (m), 1426 (m), 1348 (m); 1251 (m), 1216 (s), 1116 (s), 1025 (s), 798 (m), 646 (m), 540(w).

MS (GC-MS) *m/z* (%): 352 ($[M+H]^+$, 15), 351 ($[M]^+$ 94), 350 (47), 336 (16), 332 (13), 322 (47), 320 (24), 308 (13), 293 (18), 292 (149; 291 (13), 290 (12), 282 (35), 280 (11), 279 (14), 265 (22), 264 (40), 239 (17), 222 (10), 217 (12), 216 (100), 209 (13), 196 (11), 194 (16), 54 (11).

HRMS (EI): calcd for $C_{18}F_4H_{13}NO_2$ ($[M]^+$) 351.08769, found 351.08696.

6-fluoro-2-(4-fluorophenyl)-4-(trifluoromethyl)quinoline (10n):



Starting from 2-chloro-6-fluoro-4-(trifluoromethyl)quinoline (100 mg, 0.40 mmol), 4-fluorophenylboronic acid (67 mg, 0.48 mmol), potassium carbonate (106 mg, 0.77 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), the product **10n** was isolated as a yellow solid (109 mg, 89 %); mp = 110 – 112 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.19-7.33 (m, 2H, CH_{Ar}), 7.60 (ddd, ^3J = 9.3 Hz, ^3J = 8.0, ^4J = 2.7 Hz, 1H, CH_{Ar}), 7.71-7.80 (m, 1H, CH_{Ar}), 8.08-8.33 (m, 4 H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 108.2 (dq, $^2J_{C-F}$ = 24.3, $^4J_{C-F}$ = 2.3 Hz, CH),

116.2 (d, $^{2}J_{C\text{-}F}$ = 22.0 Hz, CH), 116.3 (q, $^{3}J_{C\text{-}F}$ = 5.5 Hz, CH), 121.0 (d, $^{2}J_{C\text{-}F}$ = 25.6 Hz, CH), 122.6 (dq, $^{3}J_{C\text{-}F}$ = 9.9 Hz, $^{3}J_{C\text{-}F}$ = 1.1 Hz, C), 123.5 (q, $^{1}J_{C\text{-}F}$ = 275.1 Hz, C), 129.5 (d, $^{3}J_{C\text{-}F}$ = 8.7 Hz, CH), 133.2 (d, $^{3}J_{C\text{-}F}$ = 9.2 Hz, CH), 135.0 (q, $^{2}J_{C\text{-}F}$ = 31.6 Hz, C), 134.4 (d, $^{4}J_{C\text{-}F}$ = 2.7 Hz, C), 146.4 (C), 155.0 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz, C), 161.3 (d, $^{1}J_{C\text{-}F}$ = 250.4 Hz, C), 164.4 (d, $^{1}J_{C\text{-}F}$ = 250.0 Hz, C).

^{19}F NMR (300 MHz, $CDCl_3$): δ = -62.16(CF_3), -109.53 (CF), -110.87 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960 (w), 2920 (w), 2850 (w), 2359 (w), 1629 (w); 1600 (w), 1557 (m), 1506 (m); 1375 (m), 1358 (br. m), 1225 (m); 1116 (br. s), 1106 (br. s), 891 (m), 860 (m); 832 (s); 788 (m), 684 (m), 585 (m), 570 (m).

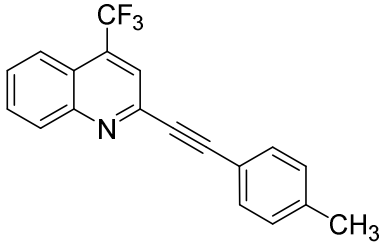
MS (GC-MS) *m/z* (%): 310 ([M+H]$^{+}$, 18), 309 ([M]$^{+}$, 100), 308 (24), 240 (47), 239 (10).

HRMS (EI): calcd for $C_{16}F_5NH_8$ ([M]$^{+}$) 309.05714, found 309.05679.

General procedure for the synthesis of compounds 11a-f:

To a Schlenk flask equipped with a magnetic stir bar $PdCl_2(PPh_3)_2$ (0.02 equiv.), CuI (0.04 equiv.) and substituted 2-chloro-4-(trifluoromethyl)quinolines **9** (100 mg) were added. The flask was fitted with a rubber septum and then held under vacuum and backfilled with argon. Afterwards THF (6 mL), corresponding acetylene (1.2 equiv.) and triethylamine (1.5 equiv.) were added successively, the reaction mixture was stirred at room temperature for 15 - 24 h. After the reaction was completed (TLC control) to the reaction mixture was added distilled water and extracted with DCM (3x25 mL), the organic layers were collected, dried over Na_2SO_4 and evaporated to crude mass; the residue was purified by column chromatography over silica gel.

2-(p-tolylethynyl)-4-(trifluoromethyl)quinoline (11a):



Starting from 2-chloro-4-(trifluoromethyl)quinoline (150 mg, 0.65 mmol), 4-methylphenylacetylene (90 mg, 0.78 mmol), $Pd(PPh_3)_2Cl_2$ (2 mol %, 9 mg, 0.01 mmol), CuI (5 mg, 0.04 equiv.), triethylamine (3 equiv., 196 mg, 1.94 mmol), the product **11a** was isolated as a brown solid (185 mg, 91 %); mp = 113 – 115 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.39 (br. s., 3H, CH_3), 7.21 (d, ^{3}J = 7.9 Hz, 2H, CH_{Ar}), 7.57 (d, ^{3}J = 8.1 Hz, 2H, CH_{Ar}), 7.68 (ddd, ^{3}J = 8.4 Hz, ^{3}J = 6.9 Hz, ^{4}J = 1.3Hz,

1H, CH_{Ar}), 7.82 (ddd, ^3J = 8.5 Hz, ^3J = 6.9 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 8.12 (d, ^3J = 8.5 Hz, 1H, CH_{Ar}), 8.22 (d, ^3J = 8.6 Hz, Hz, 1H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 21.8 (CH_3), 88.8 (C≡C), 92.1 (C≡C), 118.6, 121.6 (q, $^3J_{C\text{-}F}$ = 5.5 Hz, CH), 121.9 (q, $^3J_{C\text{-}F}$ = 1.1 Hz, C), 123.3 (q, $^1J_{C\text{-}F}$ = 275.1 Hz), 124.0 (q, $^4J_{C\text{-}F}$ = 2.3 Hz, CH), 128.8 (CH), 129.4 (CH), 130.3 (CH), 130.9 (CH), 132.4 (CH), 134.6 (q, $^2J_{C\text{-}F}$ = 31.6 Hz,), 140.2 (C), 143.4 (C), 149.2 (C);

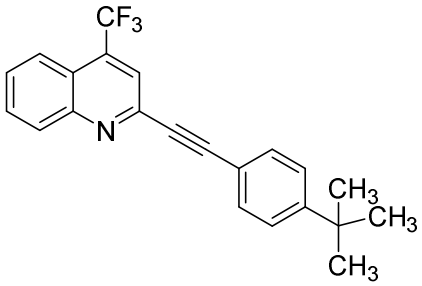
^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.61 (CF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3058 (w), 3034 (w), 3012 (w), 2962 (w), 2921 (w), 2874 (w), 2225 (m), 1941 (w), 1914 (w), 1826 (w),1767 (w),1726 (w), 1606 (m), 1512 (m), 1374 (m), 1324 (m), 1250(s), 1129 (br. s), 1024 (s), 884 (s), 817 (br. s), 763 (s), 668 (m), 539 (w).

MS (GC-MS) *m/z* (%): 312 ($[M+H]^+$, 20), 311 ($[M]^+$, 100), 310 (17), 241 (11).

HRMS (EI): calcd for $C_{19}F_3H_{12}N$ ($[M]^+$) 311.09164, found 311.09130.

2-((4-*tert*-butylphenyl)ethynyl)-4-(trifluoromethyl)quinoline (11b):



Starting from 2-chloro-4-(trifluoromethyl)quinoline (150 mg, 0.65 mmol), 1-*tert*-butyl-4-ethynylbenzene (123 mg, 0.78 mmol), $Pd(PPh_3)_2Cl_2$ (2 mol %, 9 mg, 0.01 mmol), CuI (5 mg, 0.04 equiv.), triethylamine (3 equiv., 196 mg, 1.94 mmol), the product **11b** was isolated as a brown solid (202 mg, 88 %); mp = 85 – 87 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.36 (s, 9H, C(CH_3)$_3$), 7.40-7.48 (m, 2H), 7.59-7.67 (m, 2H, CH_{Ar}), 7.67-7.73 (m, 1H, CH_{Ar}), 7.79 – 7.88 (m, 1H, CH_{Ar}), 7.90 (s, 1H, CH_{Ar}), 8.07-8.17 (m, 1H, CH_{Ar}), 8.20-8.27 (m, 1H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 31.1 (3C, 3x(CH_3)), 34.9, 88.2 (C≡C), 92.2 (C≡C), 118.6 (C), 121.7 (q, $^3J_{C\text{-}F}$ = 5.5 Hz, CH), 121.9 (q, $^3J_{C\text{-}F}$ = 1.4 Hz. C), 123.3 (q, $^1J_{C\text{-}F}$ = 274.7 Hz, C), 124.0 (q, $^4J_{C\text{-}F}$ = 2.3 Hz, CH), 125.7 (CH), 128.8 (CH), 130.3 (CH), 130.9 (CH), 132.3 (CH), 134.6 (q, $^2J_{C\text{-}F}$ = 32.0 Hz, C), 143.4 (C), 149.2 (C), 153.3 (C);

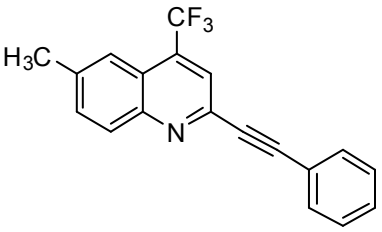
^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.60 (CF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068 (w), 2979 (w), 2932 (w), 2858 (w), 2222 (m), 2208 (m), 1605 (m); 1549 (m), 1494 (m), 1374 (s), 1259 (s), 1146 (s), 1115 (vs), 897 (m), 830 (m), 753 (s), 684 (s), 584 (m).

MS (GC-MS) *m/z* (%): 353 ($[M]^+$ 36), 339 (24), 338 (100), 310 (12), 155 (13).

HRMS (EI): calcd for $C_{22}FH_{18}N$ ($[M]^+$) 353.13859, found 353.13821.

6-methyl-2-(phenylethynyl)-4-(trifluoromethyl)quinoline (11c):



Starting from 2-chloro-6-methyl-4-(trifluoromethyl)quinoline (150 mg, 0.61 mmol), phenylacetylene (75 mg, 0.73 mmol), $Pd(PPh_3)_2Cl_2$ (2 mol %, 9 mg, 0.01 mmol), CuI (0.04 equiv., 5 mg), triethylamine (3 equiv., 185 mg, 1.83 mmol), the product **11c** was isolated as a brown solid (171 mg, 90 %); mp = 118 – 120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61 (s, CH_3), 7.31-7.45 (m, 3H, CH_{Ar}), 7.63-7.72 (m, 3H, CH_{Ar}), 7.81-7.91 (m, 2H, CH_{Ar}), 8.12 (d, ^3J = 8.7 Hz, 1H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 22.3 (CH_3), 88.7 (C≡C), 91.2 (C≡C), 123.4 (q, $^1J_{C\text{-}F}$ = 274.7 Hz), 121.6 (q, $^3J_{C\text{-}F}$ = 5.5 Hz, CH), 121.8 (C), 121.9 (q, $^3J_{C\text{-}F}$ = 1.4 Hz), 122.9 (q, $^4J_{C\text{-}F}$ = 2.0 Hz, CH), 128.6 (CH), 129.6 (CH), 130.0 (CH), 132.4 (CH), 133.2 (CH), 133.9 (q, $^2J_{C\text{-}F}$ = 31.6 Hz, C), 139.4 (C), 142.1 (C), 147.9 (C).

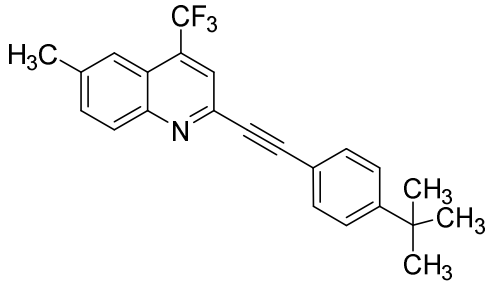
^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.67 (CF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068 (w), 3034 (w), 2979 (w), 2924 (w), 2859 (w), 2221 (m), 2209 (m), 1965 (vw), 1794 (vw), 1604 (m), 1494 (m), 1374 (s), 1274 (s), 1146 (s), 1115 (br. vs), 897 (m), 753 (s), 689 (s), 583 (w).

MS (GC-MS) *m/z* (%): 312 ($[M+H]^+$, 22), 311 ($[M]^+$ 100), 310 (19), 309 (8).

HRMS (EI): calcd for $C_{19}F_3NH_{12}$ ($[M+H]^+$) 312.09946, found 312.09986.

2-((4-*tert*-butylphenyl)ethynyl)-6-methyl-4-(trifluoromethyl)quinoline (11d):



Starting from 2-chloro-6-methyl-4-(trifluoromethyl)quinoline (150 mg, 0.61 mmol), 1-*tert*-butyl-4-ethynylbenzene (116 mg, 0.73 mmol, 1.2 equiv.), $Pd(PPh_3)_2Cl_2$ (2 mol %, 9 mg, 0.01 mmol), CuI (5 mg, 0.04 equiv.), triethylamine (185 mg, 1.83 mmol, 3 equiv.), the product **11d** was isolated as a brown solid (184 mg, 82 %); mp = 116 – 118 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (s, 9H, $C(CH_3)_3$), 2.60 (s, 3H, CH_3), 7.39-7.47 (m, 2H, CH_{Ar}), 7.58-7.70 (m, 3H, CH_{Ar}), 7.87 (s, 2H, CH_{Ar}), 8.12 (d, ^3J = 8.7 Hz, 1H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 22.3 (CH_3), 31.3 (C, $C(CH_3)_3$), 35.1(C,

$C(CH_3)_3$), 88.3 (C≡C), 91.6 (C≡C), 118.8 (C), 121.7 (q, $^3J_{C\text{-}F}$ = 5.5 Hz, CH), 121.9 (q, $^3J_{C\text{-}F}$ = 1.0 Hz), 122.9 (q, $^4J_{C\text{-}F}$ = 2.3 Hz, CH), 123.4 (q, $^1J_{C\text{-}F}$ = 274.7 Hz), 125.7 (CH), 130.0 (CH), 132.2 (CH), 133.1 (CH), 133.8 (q, $^2J_{C\text{-}F}$ = 31.6 Hz), 139.3 (C), 142.4 (C), 147.9 (C), 153.1 (C);

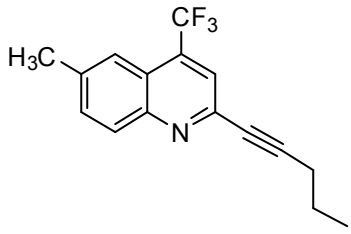
^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.60 (CF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3050 (vw), 2965 (m), 2949 (m), 2866 (w), 2201 (w), 1782 (w), 1602 (w), 1550 (w), 1507 (w), 1371 (m), 1319 (m), 1282 (m), 1254 (s), 1165 (s), 1139 (vs), 1105 (s), 825 (s), 693 (w), 648 (w), 566 (m).

MS (GC-MS) *m/z* (%): 367 (39), 353 ($[M+H\text{-}CH_3]^+$, 23), 352($[M\text{-}CH_3]^+$, 100), 324 (10), 162 (10).

HRMS (EI): calcd for $C_{23}F_3NH_{20}$ ($[M+H]^+$) 368.16206, found 368.16233.

6-methyl-2-(pent-1-ynyl)-4-(trifluoromethyl)quinoline (11e):



Starting from 2-chloro-6-methyl-4-(trifluoromethyl)quinoline (150 mg, 0.61 mmol), pent-1-yne (1.2 equiv., 50 mg, 0.73 mmol), $Pd(PPh_3)_2Cl_2$ (2 mol %, 9 mg, 0.01 mmol), CuI (5 mg, 0.04 equiv.), triethylamine (3 equiv., 185 mg, 1.83 mmol), the product **11e** was isolated as a yellow solid (155 mg, 91.6 %); mp = 118 – 120 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.09 (t, ^3J = 7.3 Hz, 3H, CH_2CH_3), 1.71 (sxt, ^3J = 7.3 Hz, 2H, $CH_2CH_2CH_3$), 2.49 (t, ^3J = 7.1 Hz, 2H, CH_2, $CH_2CH_2CH_3$), 2.58 (s, 3H, CH_3), 7.62 (dd, ^3J = 8.7 Hz, ^4J = 1.8 Hz, 1H, CH_{Ar}), 7.71 (s, 1H, CH_{Ar}), 7.83 (br. s., 1H, CH_{Ar}), 8.06 (d, ^3J = 8.7 Hz, 1H, CH_{Ar}).

^{13}C NMR (65 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 ($CH_2CH_2CH_3$), 21.9 ($CH_2CH_2CH_3$), 22.2 (Ar-CH_3), 80.7 (C≡C), 93.3 (C≡C), 121.5 (q, $^3J_{C\text{-}F}$ = 5.5 Hz, CH), 121.7 (q, $^3J_{C\text{-}F}$ = 1.2 Hz, C), 122.8 (q, $^4J_{C\text{-}F}$ = 2.0 Hz, CH), 123.4 (q, $^1J_{C\text{-}F}$ = 274.7 Hz), 129.9 (CH), 133.0 (CH), 133.7 (q, $^2J_{C\text{-}F}$ = 31.6 Hz, C), 138.9 (C), 142.6 (C), 147.7 (C).

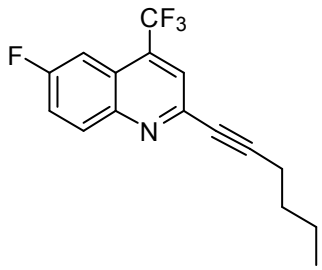
^{19}F NMR (300 MHz, $CDCl_3$): δ = -61.49 (CF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068 (w), 2979 (w), 2924 (w), 2858 (w), 2222 (m), 2208 (m), 1605 (m), 1549 (m); 1494 (m), 1374 (s), 1361 (s), 1275 (s), 1259 (s), 1146 (s), 1115 (vs), 596 (m), 830(m), 753 (s), 684 (s), 584 (m).

MS (GC-MS) *m/z* (%): 278 ($[M+H]^+$, 10), 277 ($[M]^+$, 61), 276 (19), 262 (42), 250 (16), 249 (100), 248 (27), 208 (10), 178 (15).

HRMS (EI): calcd for $C_{16}F_3H_{14}N$ ($[M]^+$) 277.10729, found 277.10708.

6-fluoro-2-(hex-1-ynyl)-4-(trifluoromethyl)quinoline (11f):



Starting from 2-chloro-6-fluoro-4-(trifluoromethyl)quinoline (150 mg, 0.61 mmol), hex-1-yne (60 mg, 0.73 mmol, 1.2 equiv.), $Pd(PPh_3)_2Cl_2$ (2 mol %, 9 mg, 0.01 mmol), CuI (0.04 equiv., 5 mg), triethylamine (185 mg, 1.82 mmol, 3 equiv.), the product **11f** was isolated as a brown solid (143 mg, 80 %), mp = 51 – 53 °C;

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.97 (t, ^3J = 7.3 Hz, 3H, CH_2CH_3), 1.41-1.77 (m, 4H, $CH_2CH_2CH_2$), 2.53 (t, ^3J = 7.0 Hz, 2H, CH_2), 7.57 (ddd, ^3J = 9.3 Hz, ^3J = 8.0 Hz, ^4J = 2.8 Hz, 1H, CH_{Ar}), 7.66-7.74 (m, 1H, CH_{Ar}), 7.76 (s, 1H, CH_{Ar}), 8.17 (dd, ^3J = 9.3 Hz, ^3J = 5.5 Hz, 1H, CH_{Ar}).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 13.6 (CH_3), 19.2 (CH_2), 22.1 (CH_2), 30.2 (CH_2), 80.1 (C≡C), 94.3 (d, $^4J_{C-F}$ = 0.9 Hz), 108.2 (dq, $^2J_{C-F}$ = 24.7 Hz, $^4J_{C-F}$ = 2.7 Hz, CH), 121.1 (d, $^2J_{C-F}$ = 25.6 Hz, CH), 122.3 (q, $^3J_{C-F}$ = 5.6 Hz, CH), 122.6 (dd, $^3J_{C-F}$ = 10.5 Hz, $^3J_{C-F}$ = 1.1 Hz, C), 123.1 (q, $^1J_{C-F}$ = 274.2 Hz, C), 132.8 (d, $^3J_{C-F}$ = 9.2 Hz, CH), 134.3 (q, $^2J_{C-F}$ = 32.0 Hz, C), 143.0 (d, $^4J_{C-F}$ = 3.2 Hz, C), 146.2 (d, ^4J = 0.9 Hz, C), 161.5 (d, $^1J_{C-F}$ = 252.2 Hz, C).

^{19}F NMR (300 MHz, $CDCl_3$): δ = -108.56 (CF), -62.31 (CF_3);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3098 (w), 3062 (w), 2956 (m), 2930 (w), 2870 (w), 2229 (m), 1626 (m), 1554 (m), 1373 (s), 1355 (s), 1250 (s), 1212 (s), 1162 (s), 1148 (s), 1123 (s), 1029 (m), 904 (s), 834 (s), 685 (s), 570 (m).

MS (GC-MS) *m/z* (%): 296 ($[M+H]^+$, 14), 295 ($[M]^+$, 75), 294 (37), 280 (59), 267 (23), 266 (100), 254 (21), 253 (87), 252 (27), 239 (21), 229 (15), 226 (13), 203 (13), 202 (18), 197 (13), 196 (18), 194 (19), 184 (12), 182 (19), 176 (13), 43 (11), 41 (16).

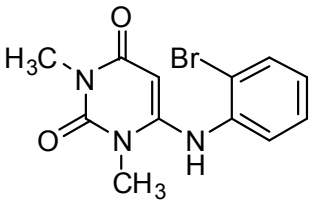
HRMS (EI): calcd for $C_{16}F_4H_{13}N$ ($[M]^+$) 295.09786, found 295.09735.

General procedure for the synthesis of compounds 13a-r:

In a Schlenk flask was prepared solution of aromatic amine (2.2 equiv.) in dry THF. Then 2.2 equiv. of *n*-BuLi (2.5 M solution in hexanes) was added at -78 °C under argon. To obtained lithium salt previously prepared solution of 6-chloro-1,3-dialkyluracil (1 equiv.) in THF was added dropwise and afterward the reaction mixture

was allowed to warm to room temperature. The next day the solution was acidified with acetic acid and the solvent was evaporated. The solid rest was triturated with water and diethyl ether, filtered off with suction, washed twice and dried in a high vacuum or purified with column chromatography.

6-(2-bromophenylamino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (13a):



Starting with 6-chloro-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 1.14 mmol), 2-bromoaniline (430 mg, 2.5 mmol) and *n*-BuLi (solution 2.5 M in hexanes) (1.2 mL, 2.5 mmol) in dry THF (5 mL), the product **13a** was isolated as a white solid (277 mg, 78 %), mp = 186-187 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.27 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 4.89 (s, 1H, N*H*), 6.47 (s, 1H, CH_{Ar}), 7.12 (ddd, ^{3}J = 8.8 Hz, ^{3}J = 6.5 Hz, ^{3}J = 2.6 Hz, 1H, CH_{Ar}), 7.27 – 7.36 (m, 2H), 7.57 – 7.64 (m, 1H, CH_{Ar});

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9 (CH_3), 29.4 (CH_3), 79.8 (CH), 119.7 (C), 126.7 (CH), 128.0 (CH), 128.7 (CH), 133.5 (CH), 135.6 (C), 151.80 (C), 151.9 (C), 163.0 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3271 (w), 2952 (w), 2916 (w), 1701 (s), 1631 (s), 1605 (s), 1580 (m), 1527 (s), 1462 (s), 1435 (s), 1379 (m), 1359 (s), 1293 (m), 1265 (m), 1248 (m), 1191 (m), 1155 (w), 1048 (m), 1025 (m), 1000 (m), 913 (w), 779 (s), 753 (s), 745 (s), 710 (w), 694 (w), 664 (m), 640 (s), 595 (w), 534 (m), 496 (s), 426 (s);

MS (GC, 70 eV) *m/z* (%): 311 ([M]$^{+}$, ^{81}Br, 36), 309 ([M]$^{+}$, ^{79}Br, 38), 230 ([M-Br]$^{+}$, 100), 212 (12), 211 (13), 210 (13), 209 (12), 173 (43), 157 (13), 155 (12), 145 (73), 130 (18), 127 (14), 117 (13), 90 (11), 82 (25), 75 (10), 55 (16), 42 (10);

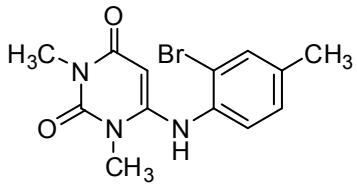
HRMS (EI): calcd. for $C_{12}H_{12}{}^{79}BrN_3O_2$ ([M]$^{+}$, ^{79}Br) 309.01074, found 309.01013;

HRMS (EI): calcd. for $C_{12}H_{12}{}^{81}BrN_3O_2$ ([M]$^{+}$, ^{81}Br) 311.00869, found 311.00704;

6-(2-bromo-4-methylphenylamino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (13b):

Starting with 6-chloro-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 1.14 mmol) and 2-bromo-4-methylaniline (470 mg, 2.5 mmol) and *n*-butyl lithium (solution 2.5 M

in hexanes) (1.2 mL, 2.5 mmol) in dry THF (5 mL), the product **13b** was isolated as a white solid (316 mg, 85 %), mp = 188-189 ºC;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 4.87 (s, 1H, N*H*), 6.23 (s, 1H, CH_{Ar}), 7.13 (dd, ^3J = 8.1 Hz, ^4J =1.0 Hz, 1H, CH_{Ar}), 7.19 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.45 (d, ^4J = 1.0 Hz, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (CH_3), 27.9 (CH_3), 29.3 (CH_3), 79.3 (CH), 119.8 (C), 126.8 (CH), 129.5 (CH), 132.7 (C), 133.8 (CH), 138.73 (C), 151.9 (C), 152.1 (C), 163.0 (C);

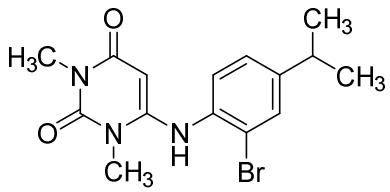
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3266 (w), 2984 (w), 2919 (w), 1688 (m), 1638 (s), 1610 (s), 1510 (s), 1462 (s), 1442 (s), 1424 (s), 1375 (s), 1359 (s), 1295 (s), 1283 (m), 1254 (m), 1208 (m), 1190 (m), 1131 (w), 1047 (m), 998 (m), 919 (w), 908 (w), 894 (w), 881 (w), 871 (w), 843 (m), 814 (m), 782 (s), 755 (s), 706 (m), 673 (m), 638 (s), 568 (m);

MS (GC, 70 eV) *m/z* (%): 326 (11), 325 ($[M]^+$, ^{81}Br, 38), 324 (15), 323 ($[M]^+$, ^{79}Br, 43), 265 (11), 245 (46), 244 ($[M-Br]^+$, 88), 242 (11), 239 (10), 224 (16), 223 (12), 210 (11), 188 (11), 187 (37), 183 (12), 160 (24), 159 (100), 146 (11), 145 (23), 144 (29), 132 (140, 131 (20), 130 (11), 127 (17), 121 (14), 117 (17), 104 (12), 103 (21), 89 (11), 88 (25), 82 (38), 79 (10), 72 (13), 63 (13), 55 (16), 41 (20);

HRMS (EI): calcd. for $C_{13}H_{14}BrN_3O_2$ ($[M]^+$, ^{79}Br) 323.02639, found 323.02616;

HRMS (EI): calcd. for $C_{13}H_{14}BrN_3O_2$ ($[M]^+$, ^{81}Br) 325.02434, found 325.02377.

6-(2-bromo-4-isopropylphenylamino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (13c):



Starting with 6-chloro-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 1.14 mmol) and 2-bromo-4-isopropylaniline (540 mg, 2.5 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (1.2 mL, 2.5 mmol) in dry THF (5 mL), the product **13c** was isolated as a white solid (282 mg, 70 %), mp = 201-202 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, ^3J = 6.92 Hz, 6H, $CH(CH_3)_2$), 2.89 (p, ^3J = 6.91 Hz, 1H, CH), 3.29 (s, 3H, CH_3), 3.58 (s, 3H, CH_3), 4.94 (s, 1H, N*H*), 6.14 (s, 1H, CH_{Ar}), 7.15 – 7.25 (m, 2H, CH_{Ar}), 7.48 (d, ^4J = 1.73 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.9 (2*CH_3), 28.1, 29.4, 33.7, 79.5 (CH), 119.9 (C), 127.0 (CH), 127.05 (CH), 131.4 (CH), 132.9 (C), 149.8 (C), 152.0 (C), 152.2 (C), 163.1 (C);

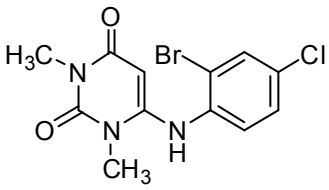
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3210 (w), 3212 (w), 3143 (w), 3061 (w), 3001 (w), 2963 (w), 2928 (w), 2874 (w), 1694 (s), 1614 (s), 1595 (s), 1575 (s), 1525 (s), 1514 (s), 1471 (m), 1450 (m), 1412 (s), 1394 (s), 1377 (s), 1365 (s), 1349 (s), 1325 (m), 1287 (s), 1236 (m), 1207 (m), 1183 (m), 1171 (m), 1156 (m), 1136 (m), 1123 (m), 1068 (m), 1049 (m), 1032 (s), 930 (w), 885 (w), 862 (w), 818 (w), 780 (s), 767 (s), 747 (s), 709 (w), 671 (m), 638 (m), 594 (m), 538 (m);

MS (GC, 70 eV) *m/z* (%): 353 ($[M]^+$, ^{81}Br, 48), 351 ($[M]^+$, ^{79}Br, 49), 339 (11), 338 (63), 337 (12), 336 (64), 273 (18), 272 ($[M-Br]^+$, 100), 320 ($[M-Br]^+$, 100), 239 (12), 237 (13), 230 (45), 226 (14), 225 (13), 224 (21), 223 (15), 215 (14), 187 (55), 172 (13), 171 (11), 158 (30), 157 (14), 145 (34), 144 (12), 143 (18), 130 (11), 127 (14), 118 (13), 117 (21), 116 (17), 115 (17), 103 (19), 102 (15), 91 917), 90 (11), 89 (15), 82 (59), 77 (17), 63 (10), 58 (31), 56 (24), 55 (34), 54 (21), 43 (18), 42 (56), 41 (19), 39 (13), 29 (12);

HRMS (EI): calcd. for $C_{15}H_{18}BrN_3O_2$ ($[M]^+$, ^{79}Br) 351.05769, found 351.05766;

HRMS (EI): calcd. for $C_{15}H_{18}BrN_3O_2$ ($[M]^+$, ^{81}Br) 353.05564, found 353.05586.

6-(2-bromo-4-chlorophenylamino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (13d):



Starting with 6-chloro-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 1.14 mmol) and 2-bromo-4-chloroaniline (520 mg, 2.5 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (1.2 mL, 2.5 mmol) in dry THF (5 mL), the product **13d** was isolated as a white solid (320 mg, 81 %), mp = 177-178 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.29 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 4.88 (s, 1H, N*H*), 6.32 (s, 1H, CH_{Ar}), 7.25 (d, ^3J = 8.7 Hz, 1H, CH_{Ar}), 7.33 (dd, ^3J = 8.6 Hz, ^4J = 2.3 Hz, 1H, CH_{Ar}), 7.64 (d, ^4J = 2.3 Hz, 1H, CH_{Ar});

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1 (CH_3), 29.7 (CH_3), 80.2 (CH), 120.1 (C), 127.3 (CH), 129.1 (CH), 132.9 (C), 133.3 (CH), 134.5 (C), 151.7 (C), 151.9 (C), 163.0 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3254 (w), 3085 (w), 2981 (w), 2951 (w), 1687 (s), 1603 (s), 1565 (s), 1530 (s), 1470 (s), 1442 (s), 1425 (s), 1384 (s), 1365 (s), 1290 (s), 1267 (m), 1255 (m), 1194 (m), 1166 (w), 1137 (w), 1096 (m), 1047 (m), 1005 (m), 915 (w),

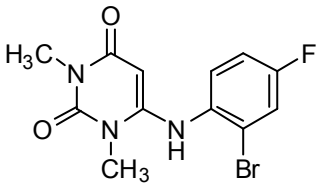
875 (w), 862 (w), 820 (m), 782 (s), 767 (s), 734 (s), 709 (m), 698 (w), 682 (m), 671 (w), 657 (m), 626 (m), 556 (s);

MS (GC, 70 eV) *m/z* (%): 347 ([M]$^+$, ^{81}Br, ^{37}Cl, 19), 346 (10), 345 ([M]$^+$, ^{79}Br, 43), 344 (15), 343 (56), 266 (33), 265 (17), 264 ([M-Br]$^+$,100), 246 (28), 245 (20), 244 (23), 243 (13), 231 (20), 229 (18), 209 (17), 207 (48), 191 (15), 189 (10), 181 (29), 180 (12), 166 (11), 164 (16), 151 (12), 127 (44), 124 (16), 82 (32), 75 (12), 55 (25), 54 (13), 42 (12);

HRMS (EI): calcd. for $C_{12}H_{11}BrClN_3O_2$ ([M]$^+$, ^{81}Br, ^{35}Cl) 344.96972, found 344.96973;

HRMS (EI): calcd. for $C_{12}H_{11}BrClN_3O_2$ ([M]$^+$, ^{81}Br, ^{37}Cl) 346.96677, found 346.96720.

6-(2-bromo-4-fluorophenylamino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (13e): Starting with 6-chloro-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 1.14 mmol) and 2-bromo-4-fluoroaniline (480 mg, 2.5 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (1.2 mL, 2.5 mmol) in dry THF (5 mL), the product **13e** was isolated as a white solid (338 mg, 90 %), mp = 160-161 °C;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.27 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 4.67 (s, 1H, N*H*), 6.45 (s, 1H, CH_{Ar}), 7.07 (ddd, ^3J = 8.8 Hz, ^3J = 7.7 Hz, ^4J = 2.8 Hz, 1H, CH_{Ar}), 7.28 (dd, ^3J = 8.8 Hz, ^4J = 4.7 Hz, 1H, CH_{Ar}), 7.39 (dd, ^3J = 7.7 Hz, ^4J = 2.8 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 28.1 (CH_3), 29.6 (CH_3), 79.2 (CH), 116.1 (d, $^2J_{C\text{-}F}$ = 22.4 Hz, CH), 120.9 (d, $^2J_{C\text{-}F}$ = 25.5 Hz, CH), 121.5 (d, $^3J_{C\text{-}F}$ = 9.2 Hz, C), 129.1 (d, ^3J = 8.9 Hz, CH), 131.9 (C), 151.9, 152.5 (C), 160.8 (d, $^1J_{C\text{-}F}$ = 252.7 Hz), 163.1 (C);

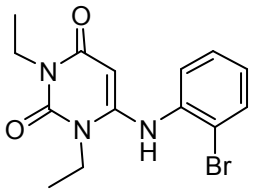
^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.23 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3244 (w), 3114 (w), 3101 (w), 3071 (w), 3043 (w), 2945 (w), 2897 (w), 1683 (s), 1603 (s), 1531 (s), 1480 (s), 1429 (s), 1379 (s), 1364 (s), 1295 (s), 1260 (s), 1226 (m), 1197 (s), 1168 (m), 1120 (m), 1061 (w), 1041 (m), 1003 (m), 947 (w), 905 (m), 863 (m), 838 9m), 811 (m), 786 (s), 759 (s), 752 (s), 716 (m), 688 (w), 670 (m), 636 (s), 579 (m), 558 (m);

MS (GC, 70 eV) *m/z* (%): 329 ([M]$^+$, ^{81}Br, 36), 327 ([M]$^+$, ^{79}Br, 36), 248 ([M-Br]$^+$, 82), 230 (22), 229 (20), 228 (23), 227 (18), 215 (17), 213 (17), 191 (42), 175 (14), 173 (12), 164 (11), 163 (100), 148 (19), 135 (20), 134 (13), 127 (22), 109 (10), 108 (29), 107 (13), 94 (27), 82 (51), 81 (11), 58 (12), 57 (16), 56 (25), 55 (32), 54 (22), 42 (37);

HRMS (EI): calcd. for $C_{12}H_{11}BrFN_3O_2$ ([M]$^+$, ^{79}Br) 327.00132, found 327.00072.

6-(2-bromophenylamino)-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione (13f):



Starting with 6-chloro-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.98 mmol) and 2-bromoaniline 2 (370 mg, 2.15 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.86 mL, 2.15 mmol) in dry THF (5 mL), the product **13f** was isolated as a white solid (304 mg, 91 %), mp = 174-176 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.44 (t, ^3J = 7.2 Hz, 3H, CH_3), 3.96 (q, ^3J = 7.0 Hz, 2H, CH_2), 4.12 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.99 (s, 1H, N*H*), 6.21 (s, 1H, CH_{Ar}), 7.06 – 7.17 (m, 1H, CH_{Ar}), 7.29 – 7.40 (m, 2H, CH_{Ar}), 7.63 (d, ^3J = 8.0 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.2 (CH_2CH_3), 14.1 (CH_2CH_3), 36.5 (CH_2CH_3), 38.1 (CH_2CH_3), 80.6 (CH), 119.1 (C), 126.3 (CH), 127.7 (CH), 128.8 (CH), 133.6 (CH), 135.7 (C), 151.2 (C), 151.3 (C), 162.8 (C);

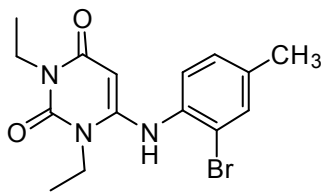
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3101 (w), 2978 (w), 2932 (w), 2872 (w), 1689 (s), 1614 (s), 1591 (s), 1574 (s), 1532 (s), 1479 (s), 1456 (s), 1435 (s), 1417 (s), 1396 (s), 1371 (s), 1336 (s), 1315 (s), 1287 (s), 1250 (m), 1216 (m), 1178 (m), 1162 (m), 1119 (w), 1094 (m), 1070 (m), 1049 (m), 1028 (m), 990 (m), 963 (w), 879 (w), 850 (w), 832 (w), 803 (w), 791 (m), 779 (s), 762 (s), 739 (s), 701 (m), 686 (m), 665 (m), 639 (s), 592 (m), 536 (m);

MS (GC, 70 eV) *m/z* (%): 339 ([M]$^+$, ^{81}Br, 16), 337 ([M]$^+$, ^{79}Br, 17), 258 ([M-Br]$^+$, 100), 198 (14), 197 (11), 196 (14), 187 (34), 171 (11), 159 (47), 157 (13), 155 (12), 144 (12), 131 (13), 117 (11), 68 (26), 29 (12);

HRMS (EI): calcd. for $C_{14}H_{16}BrN_3O_2$ ([M]$^+$, ^{79}Br) 337.04204, found 337.04223;

HRMS (EI): calcd. for $C_{14}H_{16}BrN_3O_2$ ([M]$^+$, ^{81}Br) 339.03999, found 339.04022.

6-(2-bromo-4-methylphenylamino)-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione (13g):



Starting with 6-chloro-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.98 mmol) and 2-bromo-4-methylaniline (400 mg, 2.15 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.86 mL, 2.15 mmol) in dry THF (5 mL), the product **13g** was isolated as a white solid (320 mg, 92 %), mp = 180-181 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, ^3J = 7.1 Hz, 3H, CH_3), 1.43 (t, ^3J = 7.2 Hz, 3H, CH_3), 2.34 (s, 3H, Ar-CH_3), 3.95 (q, ^3J = 7.1 Hz, 2H, CH_2), 4.11 (q,

^3J = 7.2 Hz, 2H, CH_2), 4.90 (s, 1H, N*H*), 6.10 (s, 1H, CH_{Ar}), 7.13 (dd, ^3J = 8.2 Hz, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.22 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 7.45 (d, ^4J = 1.9 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.2 (CH_2CH_3), 14.0 (CH_2CH_3), 20.8 (Ar-CH_3), 36.4 (CH_2CH_3), 37.9 (CH_2CH_3), 80.0 (CH), 119.5, 126.7 (CH), 129.5 (CH), 132.9 (C), 133.8 (CH), 138.5 (C), 151.3 (C), 151.6 (C), 162.8 (C);

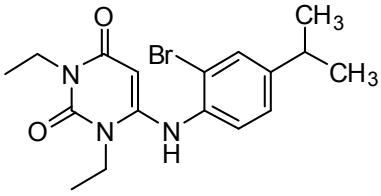
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3246 (w), 3056 (w), 2974 (w), 2932 (w), 2869 (w), 1688 (s), 1604 (s), 1593 (s), 1531 (s), 1492 (s), 1480 (s), 1457 (s), 1435 (s), 1416 (s), 1393 (s), 1373 (s), 1335 (m), 1312 (m), 1290 (s), 1267 (m), 1207 (m), 1178 (w), 1161 (w), 1089 (m), 1068 (m), 1050 (m), 1033 (m), 987 (m), 963 (w), 894 (w), 863 (w), 837 (w), 779 (s), 765 (s), 740 (s), 712 (w), 694 (w), 676 (w), 638 (m), 566 (m);

MS (GC, 70 eV) *m/z* (%): 351 ($[M]^+$, ^{79}Br, 16), 273 (35), 272 ($[M-Br]^+$, 100), 244 (13), 243 (15), 238 (13), 237 (11), 236 (11), 213 (15), 212 (27), 211 (41), 210 (20), 209 (15), 201 (29), 198 (12), 196 (12), 187 (18), 185 (18), 184 (12), 173 (74), 172 (21), 171 (11), 158 (13), 146 (17), 145 (10), 141 (18), 140 (15), 132 (15), 131 (16), 130 (15), 117 (11), 104 (11), 90 (22), 89 (29), 88 (27), 78 (16), 77 (10), 70 (12), 69 (17), 68 (13), 67 (55), 55 (19), 41 (15), 29 (16);

HRMS (ESI): calcd. for $C_{15}H_{18}BrN_3O_2$ ($[M+H]^+$, ^{79}Br) 352.06552, found 352.06541;

HRMS (ESI): calcd. for $C_{15}H_{18}BrN_3O_2$ ($[M+H]^+$, ^{81}Br) 354.06361, found 354.06350.

6-(2-bromo-4-isopropylphenylamino)-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione (13h):



Starting with 6-chloro-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.98 mmol) and 2-bromo-4-isopropylaniline (460 mg, 2.15 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.86 mL, 2.15 mmol) in dry THF (5 mL), the product **13h** was isolated as a white solid (338 mg, 90 %), mp = 191-192 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.2 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.2 (d, ^3J = 6.9 Hz, 6H, 2*CH_3), 1.41 (t, ^3J = 7.2 Hz, 3H, CH_3), 2.90 (p, ^3J = 6.9 Hz, 1H), 3.94 (q, ^3J = 7.0 Hz, 2H, CH_2), 4.11 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.91 (s, 1H, N*H*), 6.19 (s, 1H, CH_{Ar}), 7.19 (dd, ^3J = 8.3 Hz, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.21 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 7.48 (d, ^4J = 1.8 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.2 (CH_2CH_3), 14.0 (CH_2CH_3), 23.9 (CH_3), 33.7 (CH), 36.5 (CH_2CH_3), 38.0 (CH_2CH_3), 79.8 (CH), 119.8 (C), 126.9 (CH), 127.0 (CH), 131.4 (CH), 133.0 (C), 149.5 (C), 151.3 (C), 151.7 (C), 162.8 (C);

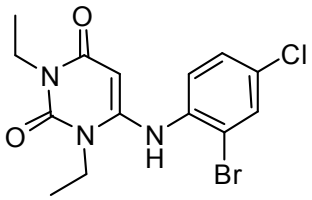
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3202 (w), 2963 (w), 2931 (w), 2871 (w), 1686 (s), 1616 (s), 1599 (s), 1587 (s), 1523 (s), 1481 (s), 1460 (m), 1452 (m), 1439 (s), 1417 (s), 1388 (s), 1381 (s), 1351 (s), 1314 (s), 1281 (s), 1246 (m), 1216 (w), 1201 (w), 1183 (w), 1169 (w), 1145 (w), 1092 (m), 1086 (m), 1068 (w), 1052 (m), 1047 (m), 1033 (m), 985 (m), 960 (w), 923 (w), 898 (m), 863 (w), 838 (w), 807 (m), 788 (m), 779 (s), 763 (s), 738 (m), 709 (m), 677 (m), 640 (m), 612 (w), 561 9m), 536 (m);

MS (GC, 70 eV) *m/z* (%): 381 ($[M]^+$, ^{81}Br, 22), 381 ($[M]^+$, ^{79}Br, 21), 301 (22), 300 ($[M-Br]^+$, 100), 258 (13), 229 (15), 224 (12), 201 (36), 159 (11), 144 (15), 68 (20), 29 (12);

HRMS (EI): calcd. for $C_{17}H_{22}BrN_3O_2$ ($[M]^+$, ^{79}Br) 379.08899, found 379.08833;

HRMS (EI): calcd. for $C_{17}H_{22}BrN_3O_2$ ($[M]^+$, ^{81}Br) 381.08694, found 381.08656.

6-(2-bromo-4-chlorophenylamino)-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione (13i):



Starting with 6-chloro-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.98 mmol) and 2-bromo-4-chloroaniline (440 mg, 2.15 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.86 mL, 2.15 mmol) in dry THF (5 mL), the product **13i** was isolated as a white solid (246 mg, 67 %), mp = 186-187 ºC;

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3), 3.95 (q, ^3J = 7.0 Hz, 2H, CH_2), 4.11 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.89 (s, 1H, N*H*), 6.28 (s, 1H, CH_{Ar}), 7.27 (d, ^3J = 8.5 Hz, 1H, CH_{Ar}), 7.32 (dd, ^3J = 8.6 Hz, ^4J = 2.2 Hz, 1H, CH_{Ar}), 7.64 (d, ^4J = 2.2 Hz, 1H, CH_{Ar});

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1 (CH_2CH_3), 14.0 (CH_2CH_3), 36.5 (CH_2CH_3), 38.0 (CH_2CH_3), 80.7 (CH), 119.7 (C), 127.0 (CH), 129.1 (CH), 132.5 (C), 133.2 (CH), 134.6 (C), 151.1 (C), 151.2 (C), 162.7 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3235 (w), 3076 (w), 3052 (w), 2974 (w), 2933 (w), 2870 (w), 1688 (s), 1613 (s), 1599 (s), 1563 (s), 1531 (s), 1475 (s), 1456 (s), 1435 (s), 1415 (s), 1394 (s), 1373 (s), 1335 (s), 1312 (s), 1289 (s), 1261 (m), 1214 (m). 1197 (m), 1177 9m), 1161 (w), 1136 (w), 1092 (s), 1068 (m), 1048 (s), 1033 (m), 988 (m), 963 (m), 885 (w), 862 (m), 830 (w), 819 (w), 801 (m), 781 (s), 765 (s), 724 (s), 691 (m), 674 (m), 628 (m), 622 (m), 556 (s), 526 (s);

MS (GC, 70 eV) *m/z* (%): 373 ($[M]^+$, ^{81}Br, ^{35}Cl, 28), 346 (10), 345 ($[M]^+$, ^{79}Br, ^{35}Cl, 21), 294 (33), 293 (16), 292 ($[M-Br]^+$,100), 258 (11), 232 (25), 231 (21), 230 (22), 229 (13), 223 (13), 221 (43), 207 (13), 205 915), 195 (17), 193 (51), 191 (12), 178 (11), 167 (20), 165 (14), 158 (10),

141 (27), 139 (13), 124 (15), 110 (10), 75 (13), 70 (18), 69 (13), 68 (45), 56 (14), 44 (12), 41 (17), 29 (32);

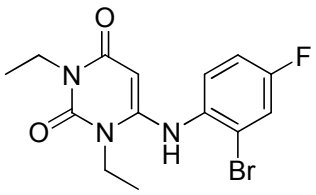
HRMS (EI): calcd. for $C_{14}H_{15}BrClN_3O_2$ ($[M]^+$, ^{79}Br, ^{35}Cl) 371.00307, found 371.00253;

HRMS (EI): calcd. for $C_{14}H_{15}BrClN_3O_2$ ($[M]^+$, ^{79}Br, ^{37}Cl) 373.00012, found 373.00042;

HRMS (EI): calcd. for $C_{14}H_{15}BrClN_3O_2$ ($[M]^+$, ^{81}Br, ^{35}Cl) 373.00102, found 373.00042;

HRMS (EI): calcd. for $C_{14}H_{15}BrClN_3O_2$ ($[M]^+$, ^{81}Br, ^{37}Cl) 374.99807, found 374.99736.

6-(2-bromo-4-fluorophenylamino)-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione (13j):



Starting with 6-chloro-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.98 mmol) and 2-bromo-4-fluoroaniline (410 mg, 2.15 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.86 mL, 2.15 mmol) in dry THF (5 mL), the product **13j** was isolated as a white solid (300 mg, 85 %), mp = 187-188 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.41 (t, ^3J = 7.2 Hz, 3H, CH_3), 3.93 (q, ^3J = 7.0 Hz, 2H, CH_2), 4.12 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.68 (s, 1H, N*H*), 6.35 (s, 1H, CH_{Ar}), 7.07 (ddd, ^3J = 8.8 Hz, ^3J = 7.7 Hz, ^4J = 2.8 Hz, 1H, CH_{Ar}), 7.29 (dd, ^3J = 8.8 Hz, ^3J = 5.3 Hz, 1H, CH_{Ar}), 7.38 (dd, ^3J = 7.7 Hz, ^4J = 2.8 Hz, 1H, CH_{Ar});

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2 (CH_2CH_3), 14.0 (CH_2CH_3), 36.5 (CH_2CH_3), 38.0 (CH_2CH_3), 79.5 (CH), 116.1 (d, $^2J_{C\text{-}F}$ = 22.5 Hz, CH), 120.8 (d, $^2J_{C\text{-}F}$ = 25.5 Hz, CH), 121.2 (d, $^3J_{C\text{-}F}$ = 9.8 Hz, C), 128.9 (d, $^3J_{C\text{-}F}$ = 8.6 Hz, CH), 132.0 (d, $^4J_{C\text{-}F}$ = 6.1 Hz), 151.1 (C), 151.9 (C), 160.7 (d, $^1J_{C\text{-}F}$ = 252.0 Hz), 162.8 (C);

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.57 (CF);

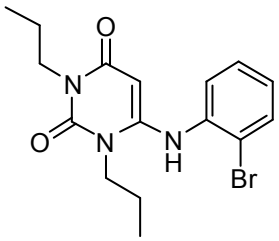
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3192 (br, w), 3060 (br, w), 2972 (br, w), 2934 (br, w), 1685 (s), 1614 (s), 1532 (s), 1487 (s), 1417 (s), 1354 (m), 1254 (m), 1191 (m), 1085 (w), 1042 (w), 982 (w), 904 (w), 787 (s), 763 (m), 696 (w), 638 (m);

MS (GC, 70 eV) *m/z* (%): 357 ($[M]^+$, ^{81}Br, 19), 355 ($[M]^+$, ^{79}Br, 20), 276 ($[M\text{-}Br]^+$, 100), 242 (10), 216 (21), 215 (19), 214 (23), 213 (15), 205 (39), 189 (13), 177 (56), 176 (10), 175 (12), 173 (10), 162 (14), 149 (15), 141 (11), 135 (14), 134 (11), 108 (22), 107 (10), 94 (20), 70 (16), 69 (11), 68 (41), 56 (19) , 44 (12), 42 (25), 41 (15), 29 (42);

HRMS (EI): calcd. for $C_{14}H_{15}BrFN_3O_2$ ($[M]^+$, ^{79}Br) 355.03262, found 355.03179;

HRMS (EI): calcd. for $C_{14}H_{15}BrFN_3O_2$ ($[M]^+$, ^{81}Br) 357.03057, found 357.03027.

6-(2-bromophenylamino)-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione (13k):



Starting with 6-chloro-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.86 mmol) and 2-bromoaniline (330 mg, 1.89 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.75 mL, 1.89 mmol) in dry THF (5 mL), the product **13k** was isolated as a white solid (289 mg, 91 %), mp = 139-140 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.04 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.63 (h, ^3J = 7.5 Hz, 2H, CH_2), 1.85 (h, ^3J = 7.4 Hz, 2H, CH_2), 3.85 (t, ^3J = 7.6 Hz, 2H, CH_2), 4.00 (t, ^3J = 7.6 Hz, 2H, CH_2), 5.01 (s, 1H, N*H*), 6.21 (s, 1H, CH_{Ar}), 7.10 (m, 1H, CH_{Ar}), 7.29-7.36 (m, 2H), 7.62 (d, ^3J = 8.1 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 11.3 (CH_3), 11.4 (CH_3), 21.2 (CH_2), 22.2 (CH_2), 43.0 (CH_2), 44.6 (CH_2), 80.6 (CH), 119.0 (C), 126.0 (CH), 127.6 (CH), 128.8 (CH), 133.6 (CH), 135.8 (C), 151.3 (C), 151.7 (C), 163.0 (C);

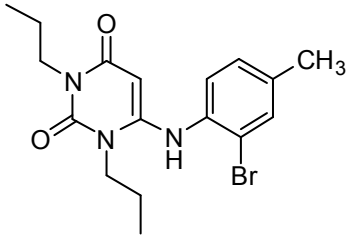
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3271 (w), 3065 (w), 2962 (w), 2933 (w), 2874 (w), 1689 (s), 1616 (s), 1600 (s), 1574 (s), 1523 (s), 1476 (s), 1437 (s), 1413 (s), 1389 (s), 1318 (m), 1304 (m), 1287 (m), 1253 (m), 1198 (m), 1176 (w), 1157 (w), 1120 (w), 1081 (w), 1055 (m), 1029 (m), 948 (w), 893 (w), 777 (s), 751 (s), 740 (s), 707 (m), 696 (w), 665 (m), 639 (s), 602 (w), 547 (s);

MS (GC, 70 eV) *m/z* (%): 367 ([M]$^+$, ^{81}Br, 31), 365 ([M]$^+$, ^{79}Br, 31), 324 (13), 287 ([(M-Br)+H]$^+$, 20), 286 ([M-Br]$^+$, 100), 244 (45), 224 (12), 222 (10), 202 (35), 201 (10), 198 (17), 197 (12), 196 (20), 195 (16), 173 (21), 171 (16), 158 (12), 157 (16), 155 (19), 131 (38), 117 (14), 68 (13), 56 (16), 43 (26), 42 (28), 41 (44), 29 (19);

HRMS (EI): calcd. for $C_{16}H_{20}{}^{79}BrN_3O_2$ ([M]$^+$) 365.07334, found 365.07306;

HRMS (EI): calcd. for $C_{17}H_{22}{}^{81}BrN_3O_2$ ([M]$^+$) 367.07129, found 367.07148.

6-(2-bromo-4-methylphenylamino)-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione (13l):



Starting with 6-chloro-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.86 mmol) and 2-bromo-4-methylaniline (350 mg 1.89 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.75 mL, 1.89 mmol) in dry THF (5 mL), the product **13l** was isolated as a white solid (290 mg, 88 %), mp = 119-120 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.5 Hz, 3H, CH_3), 1.04 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.63 (h, ^3J = 7.4 Hz, 2H, CH_2), 1.85 (h, ^3J = 7.5 Hz, 2H, CH_2),

2.34 (s, 3H, CH_3), 3.77 – 3.90 (m, 2H, CH_2), 3.90 – 4.09 (m, 2H, CH_2), 4.94 (s, 1H, N*H*), 6.04 (s, 1H, CH_{Ar}), 7.13 (dd, ^3J = 8.1 Hz, ^4J = 1.0 Hz, 1H, CH_{Ar}), 7.22 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.45 (d, ^4J = 1.0 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 11.4 (CH_3), 11.5 (CH_3), 20.8 (CH_3), 21.2 (CH_2), 22.2 (CH_2), 43.0 (CH_2), 44.5 (CH_2), 80.0 (CH), 119.3 (C), 126.4 (CH), 129.6 (CH), 132.9 (C), 133.8 (CH), 138.4 (C), 151.7 (2*C, C), 163.0 (C);

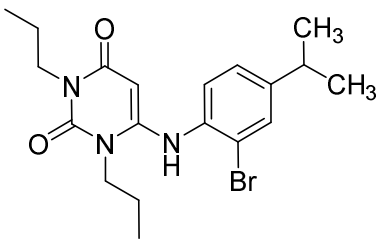
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3209 (w), 3032 (w), 2960 (w), 2927 (w), 2873 (w), 1691 (s), 1614 (s), 1519 (s), 1492 (s), 1477 (s), 1435 (s), 1414 (s), 1392 (m), 1379 (m), 1358 (m), 1340 (m), 1319 (m), 1286 (s), 1258 (m), 1205 (m), 1174 (w), 1138 (w), 1110 (w), 1078 (w), 1053 (m), 1042 (m), 1000 (w), 947 (w), 892 (w), 869 (w), 804 (m), 783 (s), 760 (s), 693 (w), 672 (m), 636 (m), 571 (m), 549 (m), 530 (m);

MS (GC, 70 eV) *m/z* (%): 381 ($[M]^+$, ^{81}Br, 31), 380 ($[M+H]^+$, ^{79}Br, 11), 379 ($[M]^+$, ^{79}Br, 31), 338 (12), 301 ($[(M-Br)+H]^+$, 20), 300 ($[M-Br]^+$, 100), 259 (12), 258 (68), 238 (12), 236 (11), 216 (34), 212 (19), 211 (17), 210 (24), 209 (13), 187 (39), 185 (30), 173 (37), 172 (14), 171 (12), 158 (14), 146 (11), 145 (58), 131 (19), 130 (14), 104 (10), 90 (21), 89 (20), 77 (13), 68 (17), 56 (20), 43 (38), 42 (37), 41 (55), 29 (21);

HRMS (EI): calcd. for $C_{17}H_{22}{}^{79}BrN_3O_2$ ($[M]^+$) 379.0899, found 379.08823;

HRMS (EI): calcd. for $C_{17}H_{22}{}^{81}BrN_3O_2$ ($[M]^+$) 381.08694, found 381.08663.

6-(2-bromo-4-isopropylphenylamino)-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione (13m):



Starting with 6-chloro-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.86 mmol) and 2-bromo-4-isopropylaniline (410 mg, 1.89 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.75 mL, 1.89 mmol) in dry THF (5 mL), the product **13m** was isolated as a white solid (283 mg, 80 %), mp = 160-161 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.04 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.25 (d, ^3J = 6.9 Hz, 6H, CH_3), 1.64 (h, ^3J = 7.4 Hz, 2H, CH_2), 1.85 (hept, ^3J = 7.4 Hz, 2H, CH_2), 2.89 (hept, ^3J = 6.9 Hz, 1H, CH), 3.71 – 3.92 (m, 2H, CH_2), 3.95 – 4.14 (m, 2H, CH_2) 4.99 (s, 1H, N*H*), 6.10 (s, 1H, CH_{Ar}), 7.19 (dd, ^3J = 8.2 Hz, ^4J = 1.7 Hz, 1H, CH_{Ar}), 7.26-7.32 (m, 1H, CH_{Ar}), 7.48 (d, ^4J = 1.7 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$) δ = 11.4 (CH_3), 11.5 (CH_3), 21.2 (CH_2), 22.2 (CH_2), 23.9 (CH_3), 33.7 (CH), 43.0 (CH_2), 44.5 (CH_2), 80.0 (CH), 119.4 (C), 126.5 (CH), 127.0 (CH), 131.4 (C), 133.1 (CH), 149.4 (C), 151.7 (2*C, C), 163.0 (C);

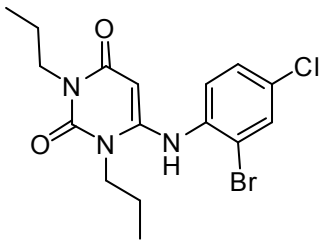
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3227 (w), 3045 (w), 2960 (w), 2930 (w), 2872 (w), 1686 (m), 1616 (s), 1603 (s), 1588 (s), 1557 (m), 1523 (s), 1477 (m), 1461 (m), 1436 (m), 1414 (m), 1390 (m), 1359 (m), 1341 (m), 1320 (m), 1305 (m), 1285 (m), 1257 (m), 1206 (w), 1175 (w), 1106 (w), 1068 (w), 1053 (m), 1040 (m), 948 (w), 926 (w), 891 (w), 878 (w), 833 (w), 780 (m), 766 (m), 736 (m), 708 (w), 676 (w), 665 (w), 636 (m), 609 (w), 546 (m);

MS (GC, 70 eV) *m/z* (%): 409 ($[M]^+$, ^{81}Br, 28), 408 ($[M+H]^+$, ^{79}Br, 10), 407 ($[M]^+$, ^{79}Br, 29), 329 ($[(M-Br)+H]^+$, 23), 328 ($[M-Br]^+$, 100), 287 (15), 286 (77), 244 (27), 240 (10), 238 (11), 224 (14), 215 (24), 213 (18), 200 (14), 198 (13), 173 (45), 159 (17), 158 (11), 144 (16), 143 (14), 117 (14), 115 (12), 103 (12), 91 (10), 68 (15), 56 (21), 43 (52), 42 (45), 41 (57), 39 (13), 29 (19);

HRMS (EI): calcd. for $C_{19}H_{26}{}^{79}BrN_3O_2$ ($[M]^+$) 407.12029, found 407.12057;

HRMS (EI): calcd. for $C_{19}H_{26}{}^{81}BrN_3O_2$ ($[M]^+$) 409.11824, found 409.11873.

6-(2-bromo-4-chlorophenylamino)-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione (13n):



Starting with 6-chloro-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.86 mmol) and 2-bromo-4-chloroaniline (390 mg, 1.89 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.75 mL, 1.89 mmol) in dry THF (5 mL), the product **13n** was isolated as a white solid (222 mg, 64 %), mp = 153 - 155 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.05 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.54-1.71 (m, 2H, CH_2), 1.84 (q, ^3J = 7.6 Hz, 2H, CH_2), 3.86 (t, ^3J = 7.9 Hz, 2H, CH_2), 4.00 (t, ^3J = 7.9 Hz, 2H, CH_2), 4.99 (s, 1H, N*H*), 6.14 (s, 1H, CH_{Ar}), 7.27-7.35 (m, 2H, CH_{Ar}), 7.61-7.66 (m, 1H, CH_{Ar});

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4 (CH_3), 11.5 (CH_3), 21.2 (CH_2), 22.3 (CH_2), 43.1 (CH_2), 44.7 (CH_2), 81.0 (CH), 126.5 (CH), 129.1 (CH), 132.3 (CH), 133.1 (C), 134.6, 151.0, 151.6, 162.9 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3240 (w), 3072 (w), 3054 (w), 2962 (w), 2932 (w), 2873 (w), 1687 (s), 1610 (s), 1593 (s), 1563 (m), 1520 (s), 1477 (s), 1436 (s), 1415 (m), 1392 (m), 1376 (m), 1359 (m), 1335 (m), 1320 (m), 1305 (m), 1276 (m), 1251 (m),

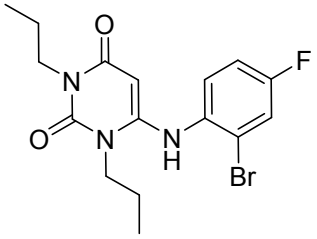
1205 (w), 1174 (w), 1142 (w), 1093 (m), 1053 (m), 1042 (m), 949 (w), 891 (m), 880 (w), 848 (w), 832 (w), 783 (s), 767 (s), 745 (w), 720 (m), 687 (w), 658 (w), 626 (m), 569 (m), 553 (m), 532 (m);

MS (GC, 70 eV) *m/z* (%): 401 ($[M]^+$, ^{81}Br, 35), 400 (($[M+H]^+$, ^{79}Br, 11), 399 ($[M]^+$, ^{79}Br, 26), 360 (15), 358 (17), 322 (34), 321 ($[(M-Br)+H]^+$, 20), 320 ($[M-Br]^+$, 100), 280 (17), 278 (51), 259 (12), 258 (16), 256 (11), 245 (12), 236 (30), 235 (14), 233 (12), 232 (34), 231 (24), 230 (30), 229 (14), 207 (29), 205 (19), 195 (32), 193 (38), 192 (11), 191 (16), 189 (11), 167 (14), 165 (41), 158 (14), 153 (18), 151 (11), 124 (12), 111 (17), 110 (13), 70 (10), 68 (21), 56 (29), 43 (45), 42 (47), 41 (75), 39 (20), 29 (30);

HRMS (ESI) calcd. for $C_{16}H_{19}{}^{79}BrClN_3O_2$ ($[M+H]^+$) 400.04219, found 400.04248;

HRMS (ESI) calcd. for $C_{16}H_{19}{}^{81}BrClN_3O_2$ ($[M+H]^+$) 402.04005, found 402.04006.

6-(2-bromo-4-fluorophenylamino)-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione (13o):



Starting with 6-chloro-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.86 mmol) and 2-bromo-4-fluoroaniline (360 mg, 1.89 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.75 mL, 1.89 mmol) in dry THF (5 mL), the product **13o** was isolated as a white solid (303 mg, 91 %), mp = 135-136 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.05 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.63 (q, ^3J = 7.6 Hz, 2H, CH_2), 1.84 (q, ^3J = 7.6 Hz, 2H, CH_2), 3.85 (t, ^3J = 7.8 Hz, 2H, CH_2), 4.01 (t, ^3J = 7.8 Hz, 2H, CH_2), 4.82 (s, 1H, N*H*), 6.06 (s, 1H, CH_{Ar}), 7.08 (ddd, ^3J = 9.1 Hz, ^3J = 7.6 Hz, ^4J = 2.9 Hz, 1H, CH_{Ar}), 7.27-7.38 (m, 1H, CH_{Ar}), 7.39 (dd, ^3J = 7.7 Hz, ^4J = 2.8 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 11.3 (CH_3), 11.4 (CH_3), 21.2 (CH_2), 22.1 (CH_2), 43.0 (CH_2), 44.5 (CH_2), 79.8 (CH), 116.1 (d, $^2J_{C\text{-}F}$ = 22.4 Hz, CH), 120.7 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, C), 120.8 (d, $^2J_{C\text{-}F}$ = 25.6 Hz, CH), 128.5 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, CH), 132.0 (d, $^4J_{C\text{-}F}$ = 3.7 Hz, C), 160.6 (d, $^1J_{C\text{-}F}$ = 252.1 Hz, C).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.86 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3224 (w), 3098 (w), 3068 (w), 3044 (w), 2961 (w), 2931 (w), 2873 (w), 1689 (s), 1614 (s), 1599 (s), 1521 (s), 1477 (s), 1435 (s), 1414 (m), 1387 (m), 1359 (m), 1338 (m), 1319 (m), 1288 (m), 1250 (s), 1190 (m), 1107 (w), 1076

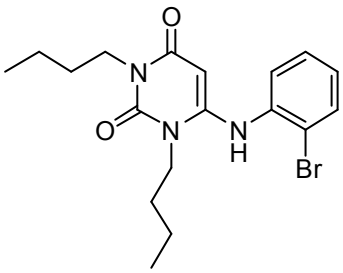
(w), 1034 (m), 947 (w), 896 (m), 858 (w), 839 (w), 812 (m), 781 (s), 759 (m), 709 (w), 688 (w), 674 (w), 633 (m), 586 (w), 549 (m);

MS (GC, 70 eV) *m/z* (%): 385 ($[M]^+$, ^{81}Br, 23), 383 ($[M]^+$, ^{79}Br, 23), 344 (10), 342 (17), 305 ($[(M-Br)+H]^+$, 23), 304 ($[M-Br]^+$, 100), 262 (46), 243 (10), 242 (15), 241 (11), 240 (14), 229 (11), 227 (11), 220 (33), 219 (13), 216 (24), 215 (21), 214 (29), 213 (16), 195 (15), 189 (19), 177 (50), 176 (12), 175 (14), 173 (12), 162 (11), 149 (42), 135 (17), 134 (14), 111 (11), 108 (17), 107 (11), 94 (19), 82 (13), 68 (20), 56 (25), 43 (37), 42 (39), 41 (63), 39 (18), 29 (27);

HRMS (ESI) calcd. for $C_{16}H_{19}{}^{79}BrFN_3O_2$ ($[M+H]^+$) 384.07174, found 384.07166;

HRMS (ESI) calcd. for $C_{16}H_{19}{}^{81}BrFN_3O_2$ ($[M+H]^+$) 386.06986, found 386.06982.

6-(2-bromophenylamino)-1,3-dibutylpyrimidine-2,4(1*H*, 3*H*)-dione (13p):



Starting with 1,3-dibutyl-6-chloropyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.77 mmol) and 2-bromoaniline (290 mg, 1.69 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.68 mL, 1.69 mmol) in dry THF (5 mL), the product **13p** was isolated as a white solid (280 mg, 92 %), mp = 132 - 133 ºC;

^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 7.3 Hz, 3H, CH_3), 0.98 (t, ^3J = 7.3 Hz, 3H, CH_3), 1.33 (q, ^3J = 7.5 Hz, 2H, CH_2), 1.44 (q, ^3J = 7.5 Hz, 2H, CH_2), 1.56 (h, ^3J = 7.3 Hz, 2H, CH_2), 1.78 (h, ^3J = 7.3 Hz, 2H, CH_2), 3.86 (t, ^3J = 7.3 Hz, 2H, CH_2), 4.03 (t, ^3J = 7.3 Hz, 2H, CH_2), 4.95 (s, 1H, N*H*), 6.35 (s, 1H, CH_{Ar}), 6.98 – 7.17 (m, 1H, CH_{Ar}), 7.28 – 7.35 (m, 2H, CH_{Ar}), 7.61 (d, ^3J = 8.4 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.88 (CH_3), 13.92 (CH_3), 20.2 (CH_2), 20.3 (CH_2), 30.0 (CH_2), 30.9 (CH_2), 41.3 (CH_2), 42.9 (CH_2), 80.5 (CH), 119.1 (C), 126.2 (CH), 127.6 (CH), 128.7 (CH), 133.5 (CH), 135.8 (C), 151.3 (C), 151.6 (C), 162.9 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3233 (w), 2955 (w), 2929 (w), 2869 (w), 1686 (m), 1619 (s), 1597 (s), 1580 (m), 1524 (s), 1497 (m), 1463 (m), 1437 (m), 1412 (m), 1391 (m), 1353 (m), 1330 (m), 1318 (m), 1290 (m), 1269 (w), 1243 (w), 1224 (w), 1190 (w), 1167 (w), 1154 (w), 1113 (w), 1081 (w), 1045 (m), 1028 (m), 949 (w), 932 (w), 910 (w), 880 (w), 812 (w), 796 (w), 779 (m), 764 (m), 739 (m), 673 (w), 665 (w), 637 (m), 602 (w), 551 (m);

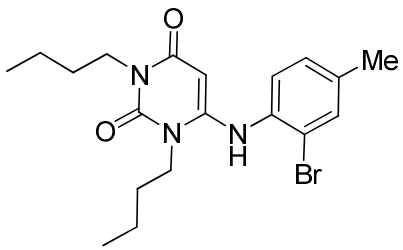
MS (GC, 70 eV) *m/z* (%): 395 ($[M]^+$, ^{81}Br, 12), 393 ($[M]^+$, ^{79}Br, 12), 378 (29), 376 (27), 340 (28), 338 (36), 315 (23), 314 ($[M-Br]^+$, 100), 272 (33), 258 (46), 225

(13), 224 (25), 223 (50), 222 (20), 216 (13), 211 (12), 209 (12), 202 (45), 198 (17), 197 (18), 196 (20), 195 (13), 173 (32), 171 (31), 159 (40), 158 (13), 157 (21), 155 (18), 145 (11), 144 (12), 117 (16), 90 (10), 77 (10), 68 (14), 57 (16), 56 (32), 55 (25), 43 (19), 42 (15), 41 (80), 39 (21), 29 (53);

HRMS (EI) calcd. for $C_{18}H_{24}{}^{79}BrN_3O_2$ ([M]$^+$) 393.10464, found 393.10385;

HRMS (EI) calcd. for $C_{18}H_{24}{}^{81}BrN_3O_2$ ([M]$^+$) 395.10259, found 395.10284.

6-(2-bromo-4-methylphenylamino)-1,3-dibutylpyrimidine-2,4(1*H*,3*H*)-dione (13q):



Starting with 1,3-dibutyl-6-chloropyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.77 mmol) and 2-bromo-4-methylaniline (310 mg, 1.69 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.68 mL, 1.69 mmol) in dry THF (5 mL), the product **13q** was isolated as a white solid (221 mg, 70 %), mp = 157-158 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 7.3 Hz, 3H, CH_3), 0.99 (t, ^3J = 7.3 Hz, 3H, CH_3), 1.33 (h, ^3J = 7.3 Hz, 2H, CH_2), 1.45 (h, ^3J = 7.3 Hz, 2H, CH_2), 1.57 (p, ^3J = 7.3 Hz, 2H, CH_2), 1.79 (p, ^3J = 7.7 Hz, 2H, CH_2), 2.34 (s, 3H, CH_3), 3.86 (t, ^3J = 7.3 Hz, 2H, CH_2), 4.02 (t, ^3J = 7.3 Hz, 2H, CH_2), 4.91 (s, 1H, N*H*), 6.15 (s, 1H, CH_{Ar}), 7.12 (dd, ^3J = 8.2 Hz, ^4J = 1.0 Hz, 1H, CH_{Ar}), 7.21 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.44 (d, ^4J = 0.9 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 13.9 (CH_3), 20.2 (CH_2), 20.3 (CH_2), 20.8 (CH_3), 41.3 (CH_2), 42.8 (CH_2), 79.9 (CH), 119.3 (C), 126.5 (CH), 129.5 (CH), 133.0 (C), 133.8 (CH), 138.3 (C), 151.7 (2*C), 162.9 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3226 (w), 3042 (w), 2956 (w), 2929 (w), 2870 (w), 1690 (s), 1616 (s), 1603 (s), 1590 (s), 1525 (s), 1489 (m), 1479 (m), 1437 (s), 1413 (m), 1391 (m), 1361 (m), 1335 (m), 1318 (m), 1289 (m), 1277 (m), 1251 (m), 1228 (w), 1192 (w), 1170 (w), 1129 (w), 1114 (w), 1080 (w), 1044 (m), 1011 (w), 950 (w), 931 (w), 911 (w), 878 (w), 836 (w), 804 (w), 778 (s), 763 (m), 745 (m), 710 (w), 692 (w), 674 (w), 634 (m), 554 (s), 526 (s);

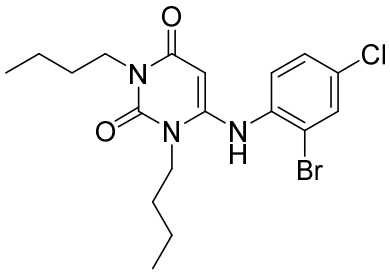
MS (GC, 70 eV) *m/z* (%): 409 ([M]$^+$, ^{81}Br, 24), 407 ([M]$^+$, ^{79}Br, 25), 392 (35), 390 (33), 354 (18), 353 (10), 352 (24), 329 (18), 328 ([M-Br]$^+$, 99), 286 (37), 273 (11), 272 (75), 239 911), 238 (24), 236 (20), 230 (14), 225 (14), 224 (10), 223 (25), 216 (57), 212 (15), 211 (25), 210 (26), 209 (17), 187 (49), 186 (15), 185 (43), 173 (37), 172 (15), 171 (16), 169 (19), 158 (14), 145 (54), 144 (11), 131 (21), 130 (17), 103

(10), 91 (13), 90 (19), 89 (18), 77 (19), 68 (17), 57 (18), 56 (40), 55 (27), 43 (19), 42 (22), 41 (100), 29 (57);

HRMS (EI) calcd. for $C_{19}H_{26}{}^{79}BrN_3O_2$ ($[M]^+$) 407.12029, found 407.11962;

HRMS (EI) calcd. for $C_{19}H_{26}{}^{81}BrN_3O_2$ ($[M]^+$) 409.11824, found 409.11832.

6-(2-bromo-4-chlorophenylamino)-1,3-dibutylpyrimidine-2,4(1*H*,3*H*)-dione (13r):



Starting with 1,3-dibutyl-6-chloropyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.77 mmol) and 2-bromo-4-chloroaniline (350 mg, 1.69 mmol) and *n*-butyl lithium (solution 2.5 M in hexanes) (0.68 mL, 1.69 mmol) in dry THF (5 mL), the product **13r** was isolated as a white solid (298 mg, 89.8 %), mp = 117-118 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 7.3 Hz, 3H, CH_3), 0.98 (t, ^3J = 7.3 Hz, 3H, CH_3), 1.33 (p, ^3J = 7.3 Hz, 2H, CH_3), 1.44 (p, ^3J = 7.3 Hz, 2H, CH_3), 1.57 (p, ^3J = 7.4 Hz, 2H, CH_2), 1.77 (p, ^3J = 7.7 Hz, 2H, CH_2), 3.86 (t, ^3J = 7.8 Hz, 2H, CH_2), 4.02 (t, ^3J = 7.8 Hz, 2H, CH_2), 4.87 (s, 1H, N*H*), 6.38 (s, 1H, CH_{Ar}), 7.25 (d, ^3J = 8.6 Hz, 1H, CH_{Ar})7.31 (dd, ^3J = 8.7 Hz, ^4J = 2.2 Hz, 1H, CH_{Ar}), 7.63 (d, ^4J = 2.2 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.89 (CH_3), 13.92 (CH_3), 20.2 (CH_2), 20.3 (CH_2), 30.0 (CH_2), 30.9 (CH_2), 41.3 (CH_2), 43.0 (CH_2), 80.7 (CH), 119.6 (C), 126.8 (CH), 129.0 (CH), 132.4 (C), 133.2 (CH), 134.7 (C), 151.1, 151.5, 162.8 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3211 (w), 2957 (w), 2929 (w), 2870 (w), 1694 (m), 1616 (s), 1594 (s), 1523 (s), 1473 (m), 1464 (m), 1437 (s), 1414 (m), 1393 (m), 1362 (m), 1335 (w), 1319 (w), 1303 (w), 1286 (m), 1259 (m), 1192 (w), 1169 (w), 1096 (m), 1042 (m), 1016 (m), 930 (w), 911 (w), 872 (w), 778 (m), 763 (m), 741 (w), 728 (w), 707 (w), 688 (w), 658 (w), 627 (w), 555 (m), 531 (m);

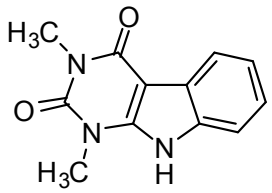
MS (GC, 70 eV) *m/z* (%): 429 ($[M]^+$, ^{81}Br, 20), 427 ($[M]^+$, ^{79}Br, 15), 414(11), 412 (28), 410 (24), 400 (10), 374 (43), 373 (11), 372 (35), 350 (30), 349 (17), 348 ($[M-Br]^+$, 88), 306 (21), 301 (11), 294 (15), 292 (48), 275 (11), 273 (11), 259 (17), 258 (22), 257 (13), 256 (15), 245 (15), 243 (11), 236 (39), 233 (12), 232 (27), 231 (29), 229 (19), 223 (65), 221 (11), 207 (35), 205 (26), 194 (11), 193 (31), 192 (11), 191 (15), 189 (10), 179 (13), 178 (11), 169 (13), 167 (20), 158 (13), 151 (12), 150 (10), 124 (17), 111 (15), 75 (11), 68 (16), 57 (21), 56 (42), 55 (31), 54 (11), 43 (24), 42 (18), 41 (100), 29 (69);

HRMS (EI) calcd. for $C_{18}H_{23}{}^{79}BrClN_3O_2$ ([M]$^+$) 427.06567, found 427.06520;
HRMS (EI) calcd. for $C_{18}H_{23}{}^{81}BrClN_3O_2$ ([M]$^+$) 429.06362, found 429.06429.

General procedure for the synthesis of 1,3-dialkyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-diones 14a-r:

To a 50 mL Schlenk flask, filled with 100 mg of corresponding 6-(2-bromoarylamino)-1,3-dialkylpyrimidine-2,4(1*H*,3*H*)-dione **13** in extra dry DMA (3 mL), $Pd(OAc)_2$ (10 mol. %), $PCy_3{\cdot}HBF_4$ (10 mol. %), DBU (2 equiv.**)** was added. The flask was fitted with a septum, and then held under vacuum for 3 min, after that it was filled with argon. Holding under vacuum was repeated one more time, and after sequent filling with argon, the reaction mixture has been stirred for 3 hours at 145°C. After completing of the reaction (TLC control), the mixture was filtered through Celite pad and filtrate was evaporated to dryness and then purified by column chromatography (EtOAc:Heptane = 1:1) to give corresponding 1,3-dialkyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-diones **14**.

1,3-dimethyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14a):



Starting with 6-(2-bromophenylamino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **13a** (100 mg, 0.32 mmol), $Pd(OAc)_2$ (7.2 mg, 10 mol %), $PCy_3{\cdot}HBF_4$ (11.9 mg, 10 mol %), DBU (2 equiv.**)**, the product **14a** was isolated as a white solid (58 mg, 78 %), mp = 346-347 ºC;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.26 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 7.09 – 7.23 (m, 2H, CH_{Ar}), 7.37 – 7.52 (m, 1H, CH_{Ar}), 7.72 – 7.91 (m, 1H, CH_{Ar}), 12.18 (s, 1H, N*H*);

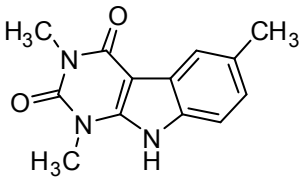
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 27.35 (CH_3), 30.7 (CH_3), 90.8 (C), 111.5 (CH), 118.6 (CH), 121.7 (CH), 122.2 (CH), 123.5 (C), 134.5 (C), 145.2 (C), 151.0 (C), 158.2 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3170 (w), 3101 (w), 2959 (w), 2925 (w), 2852 (w), 1685 (s), 1624 (s), 1605 (s), 1537 (s), 1495 (s), 1457 (s), 1441 (s), 1384 (m), 1328 (s), 1279 (m), 1259 (s), 1232 (s), 1214 (m), 1098 (s), 1057 (s), 1019 (s), 995 (s), 966 (s), 934 (w), 325 (w), 891 (w), 852 (w), 798 (s), 773 (s), 749 (s), 736 (s), 712 (s), 697 (s), 645 (s), 605 (s), 572 (m), 546 (m);

MS (GC, 70 eV) *m/z* (%): 230 ($[M+H]^+$, 13), 229 ($[M]^+$, 100), 194 (14), 172 (75), 171 (15), 162 (11), 157 (20), 144 (33), 73 (33), 57 (12), 55 (12), 44 (25), 43 (10), 42 (10), 41 (11);

HRMS (EI): calcd. for $C_{12}H_{11}N_3O_2$ ($[M]^+$) 229.08458, found 229.08486.

1,3,6-trimethyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14b):



Starting with 6-(2-bromo-4-methylphenylamino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **13b** (100 mg, 0.31 mmol), $Pd(OAc)_2$ (6.9 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (11.4 mg, 10 mol %), DBU (2 equiv.), the product **14b** was isolated as a white solid (67 mg, 89 %), mp = 347-348 ºC;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.39 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 3.4 (br.s, 1H, N*H*), 3.5 (s, 3H, CH_3, Ar-CH_3), 7.0 (dd, ^3J = 8.2 Hz, ^4J = 1.7 Hz, 1H, CH_{Ar}), 7.29 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.63 (d, ^4J = 1.7 Hz, 1H, CH_{Ar}).

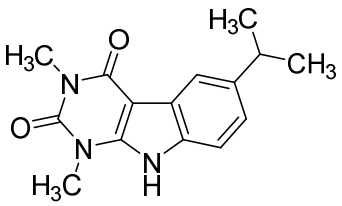
^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.2 (CH_3), 27.3 (CH_3), 30.6 (CH_3), 90.6 (C), 111.1 (CH), 118.6 (CH), 123.3 (CH), 123.8 (C), 130.4 (C), 132.8 (C), 145.2 (C), 151.0 (C), 158.2 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3408 (w), 3200 (w), 3043 (w), 2920 (w), 2855 (w), 1686 (s), 1606 (s), 1552 (m), 1536 (s), 1478 (m), 1466 (s), 1434 (m), 1417 (m), 1372 (m), 1328 (m), 1305 (m), 1282 (m), 1261 (m), 1235 (s), 1215 (m), 1201 (m), 1105 (m), 1058 (m), 1010 (m), 990 (m), 973 (s), 950 (m), 879 (w), 839 (w), 815 (s), 775 (m), 762 (m), 746 (s), 736 (m), 711 (s), 696 (s), 632 (m), 594 (m), 557 (s);

MS (GC, 70 eV) *m/z* (%): 244 ($[M+H]^+$, 16), 243 ($[M]^+$, 100), 187 (10), 186 (75), 171 (33), 158 (31), 157 (10), 116 (10);

HRMS (EI): calcd. for $C_{13}H_{13}N_3O_2$ ($[M]^+$) 243.10023, found 243.09998.

6-isopropyl-1,3-dimethyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14c):



Starting with 6-(2-bromo-4-isopropylphenylamino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **13c** (100 mg, 0.28 mmol), $Pd(OAc)_2$ (6.4 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (10.5 mg, 10 mol %), DBU (2 equiv.), the product **14c** was isolated as a white solid (68 mg, 88 %), mp = 264-265 ºC;

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.14 (d, ^3J = 6.9 Hz, 6H), 2.85 (q, ^3J = 6.9 Hz, 1H, CH), 3.30 (s, 3H), 3.46 (s, 3H), 6.94 (dd, ^3J = 8.3 Hz, ^4J = 1.8 Hz, 1H, CH_{Ar}), 7.13 (d, ^3J = 8.3 Hz, 1H, CH_{Ar}), 7.75 (d, ^4J = 1.7 Hz, 1H, CH_{Ar}), 11.28 (s, 1H, N*H*);

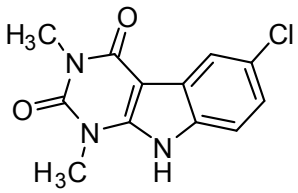
^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3 (CH_3), 27.5 (CH_3), 30.5, 34.0, 91.8 (C), 110.7 (CH), 116.9 (CH), 121.2 (CH), 123.9 (C), 132.9 (C), 142.8 (C), 145.0 (C), 151.4 (C), 159.0 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3266 (w), 3211 (w), 2956 (w), 2929 (w), 2894 (w), 2864 (w), 1702 (m), 1614 (s), 1536 (s), 1462 (s), 1436 (s), 1413 (m), 1384 (m), 1378 (m), 1349 (m), 1337 (m), 1320 (m), 1279 (m), 1268 (m), 1255 (m), 1228 (m), 1207 (m), 1154 (m), 1123 (w), 1101 (m), 1060 (m), 1045 (m), 1007 (m), 975 (s), 929 (w), 921 (w), 876 (m), 830 (w), 802 (s), 771 (s), 746 (s), 737 (s), 706 (s), 689 (m), 640 (s), 604 (m), 587 (m), 557 (m), 3536 (w);

MS (GC, 70 eV) *m/z* (%): 272 ([M+H]$^+$, 21), 271 ([M]$^+$, 100), 214 (29), 199 (80), 184 (11), 143 (12), 115 (10);

HRMS (EI): calcd. for $C_{15}H_{17}N_3O_2$ ([M]$^+$) 271.13153, found 271.13146.

6-chloro-1,3-dimethyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14d):



Starting with 6-(2-bromo-4-chlorophenylamino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **13d** (100 mg, 0.29 mmol), $Pd(OAc)_2$ (6.5 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (10.7 mg, 10 mol %), DBU (2 equiv.), the product **14d** was isolated as a white solid (69 mg, 90 %), mp = 374-375 ºC;

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.28 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 7.18 (dd, ^3J = 8.5 Hz, ^4J = 2.3 Hz, 1H, CH_{Ar}), 7.41 (d, ^3J = 8.5 Hz, 1H, CH_{Ar}), 7.77 (d, ^4J = 2.3 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, DMSO-d_6): δ = 26.9 (CH_3), 30.3 (CH_3), 90.4 (C), 112.6 (CH), 117.4 (CH), 121.5 (CH), 124.8 (C), 125.9 (C), 132.9 (C), 145.8 (C), 150.6 (C), 157.7 (C);

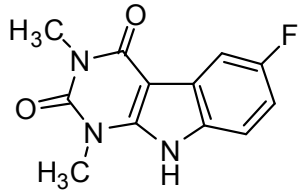
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3263 (m), 3071 (w), 2939 (w), 1761 (w), 1695 (s), 1685 (w), 1648 (s), 1622 (s), 1603 (s), 1578 (m), 1538 (s), 1495 (m), 1477 (m), 1453 (s), 1411 (m), 1391 (m), 1369 (m), 1335 (m), 1298 (m), 1277 (m), 1253 (m), 1231 (m), 1207 (m), 1151 (m), 1120 (m), 1060 (m), 1004 (m), 970 (s), 906 (m), 882 (s), 835 (m), 802 (s), 766 (s), 747 (s), 713 (s), 699 (m), 682 (s), 642 (w), 603 (s), 535 (s);

MS (GC, 70 eV) *m/z* (%): 265 ([M]$^+$, ^{37}Cl, 16), 263 ([M]$^+$, 100), 208 (25), 207 (18), 206 (73), 205 (20), 191 (25), 180 (14), 178 (41), 177 (10);

HRMS (EI): calcd. for $C_{12}H_{10}ClN_3O_2$ ([M]$^+$) 263.04561, found 263.04545;

HRMS (EI): calcd. for $C_{12}H_{10}ClN_3O_2$ ([M]$^+$,^{37}Cl) 265.04266, found 265.04273.

6-fluoro-1,3-dimethyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14e):



Starting with 6-(2-bromo-4-fluorophenylamino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **13e** (100 mg, 0.3 mmol), $Pd(OAc)_2$ (6.8 mg, 10 mol %), $PCy_3{\cdot}HBF_4$ (11.2 mg, 10 mol %), DBU (2 equiv.**)**, the product **14e** was isolated as a white solid (68 mg, 90 %), mp > 360 ºC;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.23 (s, 3H, CH_3), 3.47 (s, 3H, CH_3), 6.99 (td, ^3J = 9.3 Hz, ^4J = 2.6 Hz, 1H, CH_{Ar}), 7.37 (dd, ^3J = 8.7 Hz, ^4J = 4.4 Hz, 1H, CH_{Ar}), 7.44 (dd, ^3J = 9.3, ^4J = 2.6 Hz, 1H, CH_{Ar}), 12.21 (s, 1H, N*H*);

^{13}C NMR (126 MHz, $CDCl_3$): δ = 27.3 (CH_3), 30.7 (CH_3), 91.1 (d, $^4J_{C\text{-}F}$ = 4.1 Hz), 104.0 (d, $^2J_{C\text{-}F}$ = 25.1 Hz, CH), 109.5 (d, $^2J_{C\text{-}F}$ = 25.5 Hz, CH), 112.6 (d, $^3J_{C\text{-}F}$ = 9.7 Hz, CH), 124.3 (d, $^3J_{C\text{-}F}$ = 11.2 Hz), 130.9 (C), 146.2 (C), 150.9 (C), 158.1 (C), 158.3 (d, $^1J_{C\text{-}F}$ = 234.6 Hz);

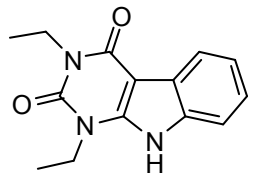
^{19}F NMR (282 MHz, DMSO-d_6): δ = -121.3 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3248 (m), 3089 (w), 3065 (w), 2922 (w), 1685 (s), 1644 (s), 1627 (s), 1604 (s), 1548 (s), 1537 (s), 1469 (s), 1455 (s), 1442 (s), 1415 (m), 1394 (m), 1371 (m), 1335 (m), 1308 (s), 1276 (m), 1253 (m), 1232 (m), 1209 (m), 1178 (s), 1164 (m), 1122 (m), 1096 (m), 1059 (m), 1003 (m), 971 (s), 936 (w), 855 (s), 836 (w), 807 (m), 788 (m), 766 (s), 746 (s), 707 (s), 686 (m), 624 (m), 560 (s);

MS (GC, 70 eV) *m/z* (%): 248 ([M+H]$^+$, 14), 247 ([M]$^+$, 100), 190 (78), 189 (28), 175 (28), 162 (62), 161 (18), 135 (15), 134 (14), 120 (13), 107 (14);

HRMS (EI): calcd. for $C_{14}H_{14}FN_3O_2$ ([M]$^+$) 247.07516, found 247.07560.

1,3-diethyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14f):



Starting with 6-(2-bromophenylamino)-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione **13f** (100 mg, 0.295 mmol), $Pd(OAc)_2$ (6.6 mg, 10 mol %), $PCy_3{\cdot}HBF_4$ (0.0109 mg, 10 mol %), DBU (2 equiv.**)**, the product **14f** was isolated as a white solid (0.07g, 92 %),

mp = 305-306 ºC;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.14 (t, ^{3}J = 7.0 Hz, 3H, CH_3), 1.2 (t, ^{3}J = 7.0 Hz, 3H, CH_3), 4.0 (q, ^{3}J = 6.9 Hz, 2H, CH_2), 4.1 (q, ^{3}J = 6.9 Hz, 2H, CH_2), 7.1–7.3 (m, 2H, CH_{Ar}), 7.4 (dd, ^{3}J = 6.2 Hz, ^{4}J = 2.8 Hz, 1H, CH_{Ar}), 7.8 (dd, ^{3}J = 6.2 Hz, ^{4}J = 2.8 Hz, 1H, CH_{Ar});

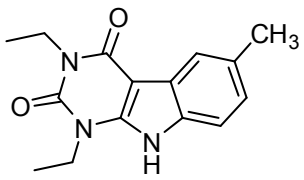
^{13}C NMR (63 MHz, DMSO-d_6): δ = 13.2 (CH_3), 13.3 (CH_3), 35.3 (CH_2), 39.0 (CH_2), 91.1 (C), 111.6 (CH), 118.6 (CH), 121.6 (CH), 122.2 (CH), 123.7 (C), 134.8 (C), 144.5 (C), 150.2 (C), 157.9 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3455 (w), 3370 (w), 3160 (w), 3099 (w), 2979 (w), 2936 (w), 2874 (w), 1683 (s), 1623 (s), 1605 (s), 1534 (s), 1497 (s), 1444 (s), 1386 (s), 1346 (m), 1319 (s), 1298 (m), 1285 (m), 1269 (s), 1241 (s), 1204 (m), 1186 (m), 1153 (m), 1141 (w), 1094 (m), 1075 (m), 1033 (m), 1015 (s), 967 (w), 922 (w), 899 (w), 875 (m), 829 (m), 790 (w), 774 (s), 751 (m), 730 (s), 703 (s), 653 (m), 643 (m), 605 M), 557 (w), 533 (m);

MS (GC, 70 eV) *m/z* (%): 258 ([M+H]$^{+}$, 31), 257 ([M]$^{+}$, 92), 187 (12), 186 (44), 185 (27), 171 (100), 169 (11), 159 (15), 158 (56), 145 (25), 144 (41), 143 (17), 130 (28), 129 (16), 117 (11), 116 (13), 103 (25), 88 (11), 87 (14), 77 (11), 29 (15);

HRMS (EI): calcd. for $C_{14}H_{15}N_3O_2$ ([M]$^{+}$) 257.11588, found 257.11636.

1,3-diethyl-6-methyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14g):



Starting with 6-(2-bromo-4-methylphenylamino)-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione **13g** (100 mg, 0.295 mmol), $Pd(OAc)_2$ (6.4 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (10.5 mg, 10 mol %), DBU (2 equiv.**)**, the product **14g** was isolated as a white solid (71 mg, 92 %), mp = 257-258 ºC;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.14 (t, ^{3}J = 6.9 Hz, 3H, CH_3), 1.27 (t, ^{3}J = 7.0 Hz, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.95 (q, ^{3}J = 6.9 Hz, 2H, CH_2), 4.1 (q, ^{3}J = 7.0 Hz, 2H, CH_2) 7.01 (dd, ^{3}J = 8.1 Hz, ^{4}J = 1.7 Hz, 1H, CH_{Ar}), 7.31 (d, ^{3}J = 8.1 Hz, 1H, CH_{Ar}), 7.65 (s, 1H, CH_{Ar}), 12.06 (s, 1H, N*H*);

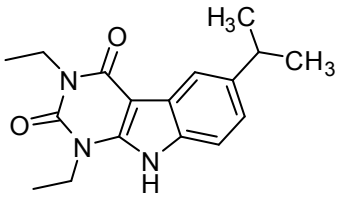
^{13}C NMR (63 MHz, DMSO-d_6): δ = 13.2 (CH_3), 13.3 (CH_3), 21.2 (CH_3), 35.3 (CH_2), 39.0 (CH_2), 90.9 (C), 111.2 (CH), 118.7 (CH), 123.4 (CH), 123.8 (C), 130.5 (C), 132.7 (C), 144.3 (C), 150.1 (C), 157.9 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3487 (w), 3388 (w), 3119 (w), 2974 (w), 2937 (w), 2873 (w), 2806 (w), 1680 (s), 1623 (s), 1601 (s), 1534 (s), 1477 (m), 1453 (s), 1447 (s), 1433 (s), 1393 (s), 1374 (m), 1352 (m), 1334 (m), 1304 (s), 1275 (s), 1249 (m), 1231 (m), 1209 (m), 1189 (m), 1133 (w), 1093 (w), 1075 (m), 1036 (w), 1015 (m), 970 (w), 929 (w), 876 (m), 847 (m), 804 (s), 787 (m), 777 (s), 750 (s), 701 (s), 677 (m), 654 (m), 615 (m), 591 (m), 562 (m), 539 (s);

MS (GC, 70 eV) *m/z* (%): 272 ($[M+H]^+$, 18), 271 ($[M]^+$, 100), 200 (41), 199 (21), 185 (59), 172 (49), 171 (25), 159 (11), 158 (19), 143 (10), 117 (12), 116 (12), 89 (12), 29 (17);

HRMS (EI): calcd. for $C_{15}H_{17}N_3O_2$ ($[M]^+$) 271.13153, found 271.13153.

1,3-diethyl-6-isopropyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14h):



Starting with 6-(2-bromo-4-isopropylphenylamino)-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione **13h** (100 mg, 0.26 mmol), $Pd(OAc)_2$ (5.9 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (9.7 mg, 10 mol %), DBU (2 equiv.), the product **14h** was isolated as a white solid (78 mg, 99 %), mp = 124-126 ºC;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.14 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.25 (d, ^3J = 6.9 Hz, 6H, CH_3), 1.27 (t, ^3J = 6.9 Hz, 3H, CH_3), 2.98 (p, ^3J = 6.9 Hz, 1H, CH), 3.96 (q, ^3J = 7.0 Hz, 2H, CH_2), 4.09 (q, ^3J = 7.0 Hz, 2H, CH_2), 7.08 (dd, ^3J = 8.3 Hz, ^4J = 1.8 Hz, 1H, CH_{Ar}), 7.34 (d, ^3J = 8.3 Hz, 1H, CH_{Ar}), 7.71 (d, ^4J = 1.8 Hz, 1H, CH_{Ar}), 12.08 (s, 1H, N*H*);

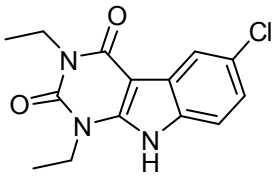
^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.2 (CH_3), 13.3 (CH_3), 24.5, 33.6, 35.3, 38.75, 91.1 (C), 111.3 (CH), 115.9 (CH), 121.2 (CH), 123.8 (C), 133.0 (C), 142.0 (C), 144.4 (C), 150.1 (C), 158.0 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3154 (w), 3071 (w), 2957 (w), 2933 (w), 2868 (w), 1690 (s), 1622 (s), 1599 (s), 1535 (s), 1470 (s), 1446 (s), 1392 (m), 1380 (m), 1344 (m), 1327 (m), 1296 (m), 1276 (s), 1266 (s), 1244 (m), 1206 (m), 1183 (w), 1151 (w), 1110 (w), 1084 (w), 1072 (m), 1030 9w), 1012 (m), 970 (w), 928 (w), 874 (w), 839 (w), 808 (m), 775 (s), 754 (s), 729 (w), 700 (s), 671 (w), 640 (m), 584 (w), 555 (w), 531 (m);

MS (GC, 70 eV) *m/z* (%): 300 ($[M+H]^+$, 20), 299 ($[M]^+$, 100), 284 (37), 228 (24), 185 (28), 184 (11);

HRMS (EI): calcd. for $C_{17}H_{21}N_3O_2$ ($[M]^+$) 299.16283, found 299.16332.

6-chloro-1,3-diethyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14i):



Starting with 6-(2-bromo-4-chlorophenylamino)-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione **13i** (100 mg, 0.268 mmol), $Pd(OAc)_2$ (6 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (9.9 mg, 10 mol %), DBU (2 equiv.**)**, the product **14i** was isolated as a white solid (70 mg, 89 %), mp = 326-328 ºC;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.14 (t, ^3J = 6.9 Hz, 3H, CH_3), 1.27 (t, ^3J = 7.0 Hz, 3H, CH_3), 3.95 (q, ^3J = 7.0 Hz, 2H, CH_2), 4.06 (q, ^3J = 7.0 Hz, 2H, CH_2), 7.20 (dd, ^3J = 8.5 Hz, ^4J = 2.2 Hz, 1H, CH_{Ar}), 7.43 (d, ^3J = 8.5 Hz, 1H, CH_{Ar}), 7.76 (d, ^4J = 2.2 Hz, 1H, CH_{Ar}), 12.39 (s, 1H, N*H*).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 13.1 (CH_3), 13.2 (CH_3), 35.4 (CH_2), 39.2 (CH_2), 90.8 (C), 113.1 (CH), 117.7 (CH), 122.1 (CH), 124.9 (C), 126.2 (C), 133.2 (C), 145.3 (C), 150.0 (C), 157.8 (C);

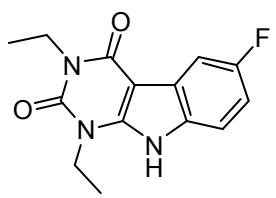
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3480 (w), 3382 (w), 3232 (w), 3117 (w), 3060 (w), 2973 (w), 2936 (w), 2872 (w), 2854 (w), 2806 (w), 1693 (s), 1674 (m), 1599 (s), 1530 (s), 1503 (m), 1481 (m), 1447 (m), 1393 (s), 1352 (m), 1334 (m), 1292 (s), 1265 (m), 1247 (s), 1230 (m), 1190 (m), 1144 (w), 1132 (w), 1116 (m), 1091 (m), 1064 (m), 1033 (w), 1014 (m), 968 (m), 873 (m), 841 9m), 805 (s), 777 (s), 749 (s), 706 (s), 695 (s), 680 (m), 664 (m), 589 (m), 555 (m), 535 (s);

MS (GC, 70 eV) *m/z* (%): 293 ($[M]^+$, 31), 291 ($[M]^+$, 100), 263 (10), 222 (14), 221 (14), 220 (40), 219 (21), 207 (17), 205 (53), 194 (16), 193 (10), 191 (13), 179 (16), 178 (19), 164 (17), 137 (17), 129 (10), 100 (11), 29 (21);

HRMS (EI): calcd. for $C_{14}H_{14}ClN_3O_2$ ($[M]^+$) 291.07691, found 291.07714;

HRMS (EI): calcd. for $C_{14}H_{14}ClN_3O_2$ ($[M]^+$, ^{37}Cl) 293.07396, found 293.07459.

1,3-diethyl-6-fluoro-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14j):



Starting with 6-(2-bromo-4-fluorophenylamino)-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione **13j** (100 mg, 0.28 mmol), $Pd(OAc)_2$ (6.3 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (10.3 mg, 10 mol %), DBU (2 equiv.**)**, the product **14j** was isolated as a white solid (73 mg, 95 %), mp = 311-312 ºC;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.17 (t, ^{3}J = 7.0 Hz, 3H, CH_3), 1.28 (t, ^{3}J = 7.0 Hz, 3H, CH_3), 4.03 (m, 4H, CH_2), 6.8 (td, ^{3}J = 9.2 Hz, ^{4}J = 2.6 Hz, 1H, CH_{Ar}), 7.20 (dd, ^{3}J = 8.5 Hz, ^{3}J = 4.2 Hz, 1H, CH_{Ar}), 7.54 (dd, ^{3}J = 9.2 Hz, ^{4}J = 2.6 Hz, 1H, CH_{Ar}), 11.64 (s, 1H, N*H*);

^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.8 (CH_3), 12.8 (CH_3), 35.4 (CH_2), 38.8 (CH_2), 91.8 (C), 104.7 (d, $^{2}J_{C\text{-}F}$ = 25.3 Hz, CH), 109.2 (d, $^{2}J_{C\text{-}F}$ = 25.5 Hz, CH), 111.4 (d, $^{3}J_{C\text{-}F}$ = 9.7 Hz, CH), 124.3 (d, $^{3}J_{C\text{-}F}$ = 11.5 Hz), 130.6, 144.7 (C), 150.0 (C), 158.1 (C), 158.3 (d, $^{1}J_{C\text{-}F}$ = 236.2 Hz, C);

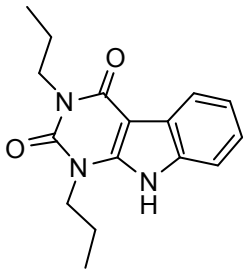
^{19}F NMR (282 MHz, DMSO-d_6): δ = -121.42 (CF);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3402 (w), 3176 (w), 2980 (w), 2964 (w), 2940 (w), 2893 (w), 2853 (w), 2798 (w), 2709 (w), 1687 (s), 1625 (s), 1604 (s), 1535 (s), 1469 (s), 1451 (s), 1400 (m), 1389 (m), 1376 (m), 1348 (m), 1333 (m), 1297 (s), 1259 (s), 1225 (m), 1205 (m), 1180 (m), 1119 (m), 1095 (m), 1080 (m), 1072 (m), 1027 (m), 1011 (m), 972 (m), 937 (m), 901 (w), 878 (w), 856 (m), 849 (m), 805 (m), 782 (s), 771 (s), 750 (m), 738 (m), 705 (s), 646 (m), 599 (m), 559 (m), 531 (s);

MS (GC, 70 eV) *m/z* (%): 276 ([M+H]$^{+}$, 16), 275 ([M]$^{+}$, 100), 247 (11), 204 (34), 203 (29), 189 (61), 176 (58), 175 (25), 163 (19), 162 (19), 148 (34), 147 (14), 134 (12), 133 (12), 121 (25), 120 (21), 107 (11), 100 (11), 29 (32) ;

HRMS (EI): calcd. for $C_{14}H_{14}FN_3O_2$ ([M]$^{+}$) 275,10646, found 275,10683.

1,3-dipropyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14k):



Starting with 6-(2-bromophenylamino)-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione **13k** (100 mg, 0.27 mmol), $Pd(OAc)_2$ (6.1 mg, 10 mol %), $PCy_3{\cdot}HBF_4$ (10.1 mg, 10 mol %), DBU (2 equiv.), the product **14k** was isolated as a white solid (58 mg, 78 %), mp = 133-134 ºC;

1H NMR (300 MHz, DMSO-d_6): δ = 0.93 (t, ^{3}J = 7.4 Hz, 3H, CH_3), 0.99 (t, ^{3}J = 7.4 Hz, 3H, CH_3), 1.64 (q, ^{3}J = 7.4 Hz, 2H), 1.75 (q, ^{3}J = 7.4 Hz, 2H), 3.93 (t, ^{3}J = 7.4 Hz, 2H), 4.04 (t, ^{3}J = 7.4 Hz, 2H), 7.19-7.34 (m, 2H, CH_{Ar}), 7.34-7.56 (m, 1H, CH_{Ar}), 7.75-8.06 (m, 1H, CH_{Ar}), 12.17 (s, 1H, N*H*);

^{13}C NMR (63 MHz, DMSO-d_6): δ = 10.7 (CH_3), 11.2 (CH_3), 20.8 (CH_2), 20.9 (CH_2), 41.7 (CH_2), 45.2 (CH_2), 91.0 (C), 111.5 (CH), 118.7 (CH), 121.7 (CH), 122.3 (CH), 123.5 (C), 134.5 (C), 144.6 (C), 150.6 (C), 158.1 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3179 (w), 2963 (w), 2933 (w), 2871 (w), 1649 (s), 1622 (s), 1601 (s), 1534 (s), 1498 (m), 1458 (m), 1444 (m), 1392 (m), 1383 (m), 1323 (m), 1284 (m), 1266 (m), 1238 (m), 1185 (w), 1165 (w), 1155 (w), 1097 (w), 1074 (m),

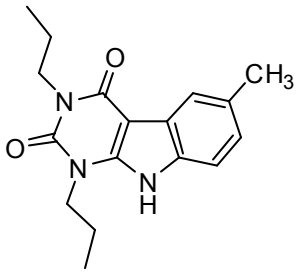
1008 (m), 947 (w), 924 (w), 881 (w), 851 (w), 826 (w), 783 (m), 774 (m), 734 (s), 703 (s), 692 (s), 647 (m), 606 (m), 570 (w), 544 (s), 526 (m);

MS (GC, 70 eV) *m/z* (%): 386 ([M]$^+$, 17), 385 ([M]$^+$, 91), 243 (41), 201 (66), 199 (14), 185 (39), 172 (27), 171 (100), 144 (14), 143 (20), 130 (16), 129 (13), 116 (22), 115 (12), 103 (20), 102 (19), 89 (11), 43 (24), 42 (14), 41 (36), 39 (18), 29 (20);

HRMS (EI): calcd. for $C_{16}H_{19}N_3O_2$ ([M]$^+$) 285.14718, found 285.14704.

6-methyl-1,3-dipropyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14l):

Starting with 6-(2-bromo-4-methylphenylamino)-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione **13l** (100 mg, 0.26 mmol) and $Pd(OAc)_2$ (6 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (9.7 mg, 10 mol %), DBU (2 equiv), the product **14l** was isolated as a white solid (68 mg, 87 %), mp = 218-219 ºC;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, ^3J = 6.5 Hz, 3H, CH_3), 1.00 (t, ^3J = 6.4 Hz, 3H, CH_3), 1.74 (h, ^3J = 6.8 Hz, 2H), 1.86 (h, ^3J = 6.7 Hz, 2H), 2.35 (s, 3H, CH_3), 4.08 (m, 4H), 7.00 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.23 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 7.84 (s, 1H, CH_{Ar}), 9.56 (s, 1H, N*H*);

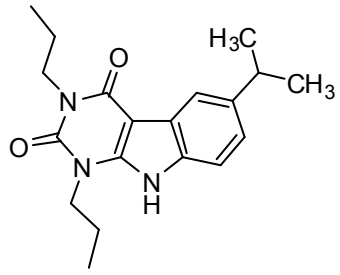
^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1 (CH_3), 11.4 (CH_3), 21.4, 21.4, 21.5, 43.0, 45.8, 92.5 (C), 110.7 (CH), 120.0 (CH), 124.1, 124.3 (CH), 132.3 (C), 132.4 (C), 144.5 (C), 151.1 (C), 159.5 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3217 (w), 3158 (w), 2958 (w), 2930 (w), 2869 (w), 1691 (s), 1619 (s), 1604 (s), 1583 (s), 1550 (m), 1536 (s), 1474 (m), 1461 (m), 1428 (m), 1393 (m), 1377 (m), 1361 (m), 1334 (m), 1305 (m), 1270 (m), 1238 (m), 1230 (m), 1197 (m), 1183 (m), 1130 (w), 1108 (w), 1082 (m), 1038 (m), 979 (m), 943 (w), 932 (w), 898 (w), 885 (w), 873 (m), 833 (m), 792 (s), 773 (s), 751 (m), 739 (m), 707 (s), 654 (m), 574 (s), 526 (m);

MS (GC, 70 eV) *m/z* (%): 300 ([M]$^+$, 15), 299 ([M]$^+$, 72), 257 (45), 215 (41), 214 (14), 199 (25), 186 (24), 185 (100), 184 (12), 172 (32), 171 (22), 170 (11), 158 (11), 144 (11), 142 (16), 117 (14), 116 (13), 89 (13), 43 (25), 42 (16), 41 (33), 39 (11), 29 (16);

HRMS (EI): calcd. for $C_{17}H_{21}N_3O_2$ ([M]$^+$) 299.16283, found 299.16231.

6-isopropyl-1,3-dipropyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14m):



Starting with 6-(2-bromo-4-isopropylphenylamino)-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione **13m** (100 mg, 0.24 mmol), $Pd(OAc)_2$ (5.5 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (9 mg, 10 mol %), DBU (2 equiv.), the product **14m** was isolated as a white solid (75 mg, 93 %), mp = 89-90 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97-1.01 (m, 6H, CH_3), 1.12 (d, ^3J = 6.9 Hz, 6H, CH_3), 1.69-1.93 (m, 4H), 2.86 (p, ^3J = 6.9 Hz, 1H), 4.06-4.20 (m, 4H), 7.02 (dd, ^3J = 8.4 Hz, ^4J = 1.7 Hz, 1H, CH_{Ar}), 7.26 (d, ^3J = 8.4 Hz, 1H, CH_{Ar}), 7.88 (d, ^4J = 1.6 Hz, 1H, CH_{Ar}), 10.31 (s, 1H, N*H*);

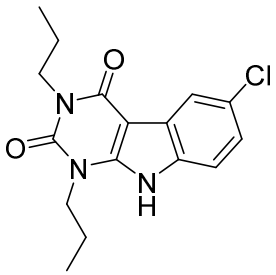
^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.0, 11.4, 21.5, 21.5, 24.3, 34.2, 43.0, 45.9, 92.6 (C), 111.0 (CH), 117.1 (CH), 122.1 (CH), 124.0 (C), 132.8 (C), 143.7 (C), 144.8 (C), 151.1 (C), 159.7 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3155 (w), 3071 (w), 2958 (m), 2930 (w), 2871 (w), 1692 (s), 1621 (s), 1598 (s), 1534 (s), 1470 (s), 1458 (s), 1430 (m), 1393 (m), 1381 (m), 1361 (m), 1343 (m), 1327 (m), 1278 (m), 1260 (m), 1238 (m), 1197 (m), 1180 (m), 1107 (m), 1078 (m), 1038 (m), 977 (w), 968 (w), 920 (w), 881 (m), 855 (w), 807 (m), 776 (m), 752 (m), 702 (m), 640 (m), 572 (m), 533 (m);

MS (GC, 70 eV) *m/z* (%): 328 ($[M+H]^+$, 18), 327 ($[M]^+$, 100), 326 (12), 312 (18), 286 (12), 285 (53), 270 (34), 243 (27), 242 (15), 241 (10), 228 (18), 227 (22), 214 (19), 213 (76), 211 (14), 199 (10), 197 (17), 185 (35), 184 (15), 171 (10), 158 (13), 156 (12), 115 (18), 56 (10), 43 (39), 42 (29), 41 (46), 39 (10), 29 (11);

HRMS (EI): calcd. for $C_{19}H_{25}N_3O_2$ ($[M]^+$) 327.19413, found 327.19367.

6-chloro-1,3-dipropyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14n):



Starting with 6-(2-bromo-4-chlorophenylamino)-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione **13n** (100 mg, 0.25 mmol) and $Pd(OAc)_2$ (5.6 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (9.2 mg, 10 mol %), DBU (2 equiv), the product **14n** was isolated as a white solid (38 mg, 48 %), mp = 230-231 ºC;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.87 (t, ^3J = 7.5 Hz, 3H, CH_3), 0.93 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.58 (q, ^3J = 7.4 Hz, 2H), 1.70 (q, ^3J = 7.5 Hz, 2H), 3.86 (t, ^3J = 7.5 Hz, 2H), 3.97 (t, ^3J = 7.5 Hz, 2H), 7.20 (dd, ^3J = 8.5 Hz, ^4J = 2.2 Hz, 1H, CH_{Ar}), 7.43 (d, ^3J = 8.5 Hz, 1H, CH_{Ar}), 7.76 (d, ^4J = 2.2 Hz, 1H, CH_{Ar}), 12.35 (s, 1H, N*H*);

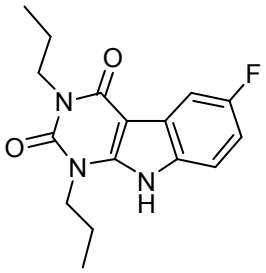
^{13}C NMR (63 MHz, DMSO-d_6): δ = 10.7 (CH_3), 11.1 (CH_3), 20.7, 20.8, 41.7, 45.3, 90.6 (C), 113.0 (CH), 117.7 (CH), 122.1 (CH), 124.8 (C), 126.1 (C), 133.1 (C), 145.4 (C), 150.4 (C), 157.9 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3501 (w), 2458 (w), 3121 (w), 3079 (w), 2956 (w), 2938 (w), 2877 (w), 1680 (s), 1650 (s), 1620 (s), 1600 (s), 1553 (m), 1539 (s), 1463 (m), 1449 (s), 1426 (w), 1389 (m), 1373 (w), 1365 (w), 1336 (m), 1291 (s), 1259 (m), 1244 (m), 1199 (w), 1180 (w), 1143 (w), 1080 (s), 1042 (s), 976 (m), 929 (m), 893 (w), 873 (m), 835 (w), 802 (s0, 771 (s), 748 (s), 732 (m), 709 (s), 678 (w), 652 (w), 576 (s), 559 (s);

MS (GC, 70 eV) *m/z* (%): 320 ([M+H]$^+$, 18), 319 ([M]$^+$, 100), 279 (13), 278 (13), 277 (43), 237 (27), 235 (85), 233 (12), 221 (13), 219 (37), 218 (10), 207 (34), 206 (30), 205 (90), 194 (18) 193 (10), 192 (47), 191 (17), 178 (14), 177 (11), 170 (12), 169 (10), 164 (16), 142 (20), 137 (18), 129 (12), 102 (10), 56 (15), 43 (40), 42 (25), 41 (60), 39 (21), 29 (22);

HRMS (EI): calcd. for $C_{19}H_{25}ClN_3O_2$ ([M]$^+$) 319.10821, found 319.10770.

6-fluoro-1,3-dipropyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14o):



Starting with 6-(2-bromo-4-fluorophenylamino)-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione **13o** (100 mg, 0.26 mmol) and $Pd(OAc)_2$ (5.8 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (9.6 mg, 10 mol %), DBU (2 equiv.**)**, the product **14o** was isolated as a white solid (65 mg, 82 %), mp = 228-229 ºC;

^{1}H NMR (300 MHz, Acetone-d_6): δ = 0.89 (t, ^3J = 7.5 Hz, 3H, CH_3), 0.94 (t, ^3J = 7.5 Hz, 3H, CH_3), 1.63 (h, ^3J = 7.5 Hz, 2H), 1.79 (h, ^3J = 7.4 Hz, 2H), 3.79 – 3.86 (m, 2H), 3.91 – 3.98 (m, 2H), 6.91 (ddd, ^3J = 9.6 Hz, ^3J = 8.8 Hz, ^4J = 2.6 Hz, 1H, CH_{Ar}), 7.33 (ddd, ^3J = 8.8 Hz, ^3J = 4.3 Hz, ^4J = 0.5 Hz, 1H, CH_{Ar}), 7.56 (dd, ^3J = 9.3 Hz, ^4J = 2.6 Hz, 1H, CH_{Ar}), 11.11 (s, 1H, N*H*);

^{13}C NMR (63 MHz, Acetone-d_6): δ = 11.3 (CH_3), 11.7 (CH_3), 22.1, 22.1, 43.0, 46.4, 93.1 (d, $^4J_{C\text{-}F}$ = 4.0 Hz), 105.7 (d, $^2J_{C\text{-}F}$ = 25.6 Hz, CH), 110.6 (d, $^2J_{C\text{-}F}$ = 25.8 Hz, CH), 113.2 (d, $^3J_{C\text{-}F}$ = 9.7 Hz, CH), 126.2 (d, $^3J_{C\text{-}F}$ = 11.2 Hz), 132.0 (C), 146.8 (C), 151.9 (C), 159.3 (C), 160.1 (d, $^1J_{C\text{-}F}$ = 235.4 Hz);

^{19}F NMR (282 MHz, $CDCl_3$): δ = -122.69 (CF);

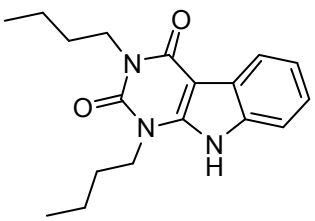
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3218 (w), 3194 (w), 2959 (w), 2932 (w), 2875 (w), 2851 (w), 1693 (s), 1628 (s), 1601 (s), 1535 (s), 1468 (s), 1455 (s), 1429 (m), 1394 (m),

1363 (m), 1335 (w), 1302 (s), 1292 (s), 1257 (s), 1199 (w), 1179 (m), 1167 (m), 1097 (m), 1077 (m), 1036 (s), 978 (m), 963 (m), 954 (m), 915 (w), 891 (w), 854 (m), 797 (s), 771 (s), 750 (s), 698 (s), 668 (w), 636 (m), 568 (s), 526 (s);

MS (GC, 70 eV) *m/z* (%): 304 ($[M+H]^+$, 14), 303 ($[M]^+$, 75), 261 (28), 219 (61), 218 (10), 217 (11), 203 (28), 190 (24), 189 (100), 176 (37), 175 (15), 162 (12), 161 (17), 148 (15), 147 (13), 134 (16), 133 (11), 121 (17), 120 (13), 107 (11), 43 (22), 42 (16), 41 (32), 29 (14);

HRMS (EI): calcd. for $C_{16}H_{18}FN_3O_2$ ($[M]^+$) 303.13776, found 303.13826.

1,3-dibutyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14p):



Starting with 6-(2-bromophenylamino)-1,3-dibutylpyrimidine-2,4(1*H*,3*H*)-dione **13p** (100 mg, 0.25 mmol) and $Pd(OAc)_2$ (5.7 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (9.3 mg, 10 mol %), DBU (2 equiv.**)**, the product **14p** was isolated as a white solid (66 mg, 83 %), mp = 227-228 ºC;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.91 (t, ^3J = 7.3 Hz, 3H, CH_3), 0.93 (t, ^3J = 7.3 Hz, 3H, CH_3), 1.33 (m, 4H), 1.55 (p, ^3J = 7.2 Hz, 2H), 1.66 (p, ^3J = 7.2 Hz, 2H), 3.91 (t, ^3J = 7.5 Hz, 2H), 4.03 (t, ^3J = 7.5 Hz, 2H), 7.15 – 7.26 (m, 2H), 7.40 – 7.48 (m, 1H, CH_{Ar}), 7.78 – 7.90 (m, 1H, CH_{Ar}), 12.14 (s, 1H, N*H*);

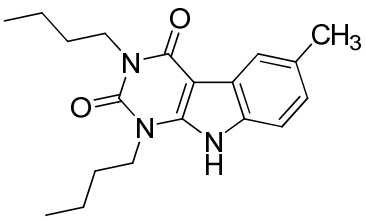
^{13}C NMR (63 MHz, DMSO-d_6): δ = 13.6 (CH_3), 13.7 (CH_3), 19.3, 19.6, 29.6, 29.7, 39.9, 43.6, 91.0 (C), 111.5 (CH), 118.6 (CH), 121.7 (CH), 122.2 (CH), 123.5 (C), 134.5 (C), 144.5 (C), 150.4 (C), 158.0 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3188 (w), 2957 (w), 2932 (w), 2865 (w), 1686 (s), 1626 (s), 1601 (s), 1581 (w), 1535 (s), 1495 (m), 1459 (m), 1428 (w), 1408 (w), 1394 (w), 1376 (w), 1323 (m), 1292 (w), 1269 (m), 1232 (m), 1190 (w), 1149 (w), 1115 (w), 1084 (m), 1049 (w), 1018 (w), 1010 (w), 968 (w), 928 (m), 905 (w), 832 (w), 811 (w), 775 (s), 751 (s), 738 (m), 703 (m), 645 (m), 605 (m), 5689 (m), 557 (m), 537 (m);

MS (GC, 70 eV) *m/z* (%): 314 ($[M+H]^+$, 17), 313 ($[M]^+$, 79), 257 (29), 240 (28), 215 (36), 201 (51), 185 (44), 172 (34), 171 (100), 158 (46), 157 (15), 130 (13), 116 (16), 103 (14), 41 (12), 29 (10);

HRMS (EI) calcd. for $C_{18}H_{23}N_3O_2$ ($[M]^+$) 313.17848, found 313.17862.

1,3-dibutyl-6-methyl-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14q):



Starting with 6-(2-bromo-4-methylphenylamino)-1,3-dibutylpyrimidine-2,4(1*H*,3*H*)-dione **13q** (100 mg, 0.245 mmol) and $Pd(OAc)_2$ (5.5 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (9 mg, 10 mol %), DBU (2 equiv.**)**, the product **14q** was isolated as a white solid (69.7 mg, 87 %), mp = 175-176 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 7.3 Hz, 3H, CH_3), 0.92 (t, ^3J = 7.3 Hz, 3H, CH_3), 1.28 – 1.51 (m, 4H), 1.61 – 1.72 (m, 2H), 1.74 – 1.91 (m, 2H), 2.33 (s, 3H, CH_3), 4.0 – 4.22 (m, 4H), 7.00 (dd, ^3J = 8.3 Hz, ^4J = 1.6 Hz, 1H, CH_{Ar}), 7.24 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 7.82 (s, 1H, CH_{Ar}), 9.85 (s, 1H, N*H*);

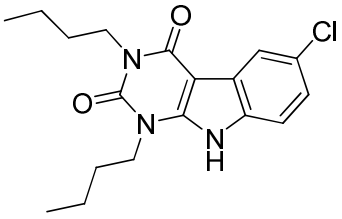
^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.7(CH_3), 13.8(CH_3), 20.0 (CH_2), 20.3 (CH_2), 21.4(CH_3), 30.3 (2*CH_2), 41.3 (CH_2), 44.3 (CH_2), 92.5 (C), 110.8 (CH), 119.9 (CH), 124.0, 124.3 (CH), 132.3 (C), 132.4 (C), 144.6 (C), 151.0 (C), 159.5 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3220 (w), 3183 (w), 2953 (w), 2927 (w), 2869 (w), 1687 (s), 1604 (s), 1537 (s), 1473 (m), 1463 (m), 1434 (m), 1393 (m), 1366 (m), 1335 (m), 1301 (m), 1271 (m), 1234 (m), 1190 (w), 1175 (w), 1116 (w), 1084 (m), 1047 (w), 1020 (w), 967 (w), 949 (w), 931 (w), 900 (w), 871 (w), 840 (w), 794 (s), 773 (s), 753 (m), 735 (m), 701 (m), 641 (m), 566 (m);

MS (GC, 70 eV) *m/z* (%): 328 ($[M+H]^+$, 20), 327 ($[M]^+$, 93), 311 (15), 310 (69), 271 (34), 215 (42), 199 (42), 186 (35), 185 (100), 172 (46), 171 (24), 158 (11), 144 (10), 142 (15), 117 (10);

HRMS (EI) calcd. for $C_{19}H_{25}N_3O_2$ ($[M]^+$) 327.19413, found 327.19395.

1,3-dibutyl-6-chloro-1*H*-pyrimido[4,5-*b*]indole-2,4(3*H*,9*H*)-dione (14r):



Starting with 6-(2-bromo-4-chlorophenylamino)-1,3-dibutylpyrimidine-2,4(1*H*,3*H*)-dione **13r** (100 mg, 0.23 mmol) and $Pd(OAc)_2$ (5.2 mg, 10 mol %), $PCy_3 \cdot HBF_4$ (8.6 mg, 10 mol. %), DBU (2 equiv**)**, the product **14r** was isolated as a white solid (35 mg, 43 %), mp = 225-226 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 – 0.99 (m, 6H), 1.27 – 1.49 (m, 4H), 1.56 – 1.74 (m, 2H), 1.72 – 1.89 (m, 2H), 4.01 – 4.19 (m, 4H), 7.13 (dd, ^3J = 8.5 Hz, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.24 (d, ^3J = 8.5 Hz, 1H, CH_{Ar}), 7.98 (d, ^4J = 1.9 Hz, 1H, CH_{Ar}), 9.88 (s, 1H, N*H*);

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 13.9 (CH_3), 20.2 (CH_2), 20.4 (CH_2), 30.4 (CH_2), 30.4 (CH_2), 41.5 (CH_2), 44.6 (CH_2), 92.6 (C), 112.3 (CH), 119.7 (CH), 123.4 (CH), 125.2 (C), 128.6 (C), 132.8 (C), 145.3 (C), 151.0 (C), 159.4 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3159 (w), 2956 (w), 2928 (w), 2870 (w), 2860 (w), 1695 (s), 1626 (s), 1598 (s), 1550 (m), 1533 (s), 1478 (m), 1459 (m), 1446 (s), 1391 (ms), 1369 (m), 1334 (m), 1287 (s), 1260 (s), 1232 (m), 1188 (w), 1173 (w), 1140 (w), 1113 (w), 1084 (m), 1043 (m), 1020 (w), 954 (m), 944 (m), 931 (m), 908 (m), 865 (m), 842 (m), 800 (m), 774 (s), 751 (m), 707 (m), 699 (m), 650 (m), 588 (m), 573 (m), 554 (m);

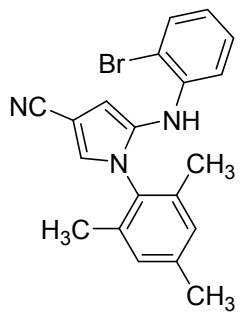
MS (GC, 70 eV) *m/z* (%): 349 (28), 348 (17), 347 ($[M]^+$, 85), 332 (30), 331 (18), 330 (85), 305 (12), 293 (14), 292 (11), 291 (41), 276 (12), 274 (32), 251 (13), 249 (40), 237 (21), 236 (11), 235 (63), 221 (17), 220 (10), 219 (47), 208 (13), 207 (36), 206 (37), 205 (100), 194 (19), 193 (14), 192 (53), 191 (15), 178 (13), 164 (13), 142 (22), 137 (11), 41 (24), 29 (19);

HRMS (EI) calcd. for $C_{18}H_{22}ClN_3O_2$ $[M]^+$ 347.13951, found 347.13937.

General procedures for the synthesis of 16a-r:

To a pressure tube equipped with stirrer bar, 100 mg of N-substituted aminopyrrole **15**, corresponding amounts of bromoarene (1.1 equiv.), $Pd(OAc)_2$ (5 mol. %), DPEphos (10 mol. %) and Cs_2CO_3 (2.5 equiv.) were dissolved in extra dry 1,4-dioxane (4 mL) under inert atmosphere. The mixture was heated at 110 ºC for 10-12h. Upon completion (TLC control), the reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography.

5-(2-bromophenylamino)-1-mesityl-1*H*-pyrrole-3-carbonitrile (16a):



Starting with **15** (100 mg, 0.44 mmol), bromoarene (115 mg, 1.1 equiv.), $Pd(OAc)_2$ (4.9 mg, 5 mol. %), DPEphos (24 mg, 10 mol. %), Cs_2CO_3 (361 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16a** was isolated as a brown solid (113 mg, 67 %). mp = 64-65 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.0 (s, 6H, 2*CH_3), 2.3 (s, 3H, CH_3), 5.5 (s, 1H, N*H*), 6.3 (dd, ^4J = 1.9 Hz, 1H, CH_{Ar}), 6.7 (ddd, ^3J = 7.9 Hz, ^3J = 7.0 Hz, ^3J = 1.9 Hz, 1H, CH_{Ar}), 6.9 (d, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.0 (s, 2H,

CH_{Ar}), 7.1 (dd, ^3J = 8.2 Hz, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.2 (ddd, ^3J = 8.4 Hz, ^3J = 6.9 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 7.4 (dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.6 (2*C, CH_3), 21.2 (CH_3), 92.6 (C), 100.8 (C), 110.7 (CH), 114.6 (CH), 116.9 (C), 121.2 (CH), 124.7 (CH), 128.6 (CH), 129.5 (CH), 131.8 (C), 131.9 (C), 132.7 (CH), 136.2 (C), 139.8 (C), 140.9 (C);

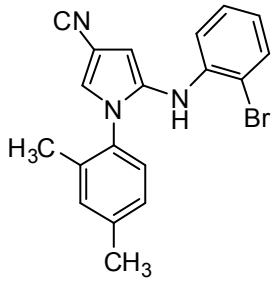
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3742 (w), 3363 (w), 3129 (w), 3063 (w), 3021 (w), 2950 (w), 2919 (w), 2856 (w), 2736 (w), 2596 (w), 2327 (w), 2223 (s), 2173 (w), 1898 (w), 1684 (w), 1592 (s), 1580 (s), 1565 (s), 1511 (s), 1488 (s), 1455 (m), 1439 (s), 1375 (m), 1300 (s), 1238 (m), 1217 (m), 1180 (m), 1157 (m), 1143 (m), 1118 (w), 1043 (m), 1022 (s), 977 (m), 948 (w), 932 (w), 852 (m), 801 (m), 746 (s), 706 (w), 692 (w), 673 (w), 657 (w), 637 (m), 584 (m), 553 (m);

MS (GC, 70 eV) *m/z* (%): 382 (23), 381 ([M]$^+$, ^{81}Br, 99), 380 (26), 379 ([M]$^+$, ^{79}Br, 100), 364 (12), 300 (16), 209 (41), 193 (14), 182 (12), 155 (14), 120 (11), 119 (11), 105 (11), 91 (15), 77 (15);

HRMS (EI) calcd for $C_{20}H_{18}N_3Br$ ([M]$^+$, ^{79}Br) 379.06786, found 379.06738;

HRMS (EI) calcd for $C_{20}H_{18}N_3Br$ ([M]$^+$, ^{81}Br) 381.06582, found 381.06555.

5-(2-bromophenylamino)-1-(2, 4-dimethylphenyl)-1*H*-pyrrole-3-carbonitrile (16b):



Starting with **15** (100 mg, 0.47 mmol), bromoarene (122 mg, 1.1 equiv.), $Pd(OAc)_2$ (5.3 mg, 5 mol%), DPEphos (25.4 mg, 10 mol%), Cs_2CO_3 (385 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16b** was isolated as a brown solid (156 mg, 90 %). mp = 83-84 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 5.63 (s, 1H, N*H*), 6.36 (dd, ^4J = 1.9 Hz, ^5J = 0.9 Hz, 1H, CH_{Ar}), 6.67 (ddd, ^3J = 8.0 Hz, 7.3 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 6.91 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.02-7.04 (m, 2H, CH_{Ar}), 7.09 (d, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.10 – 7.19 (m, 2H, CH_{Ar}), 7.36 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.4 (CH_3), 21.3 (CH_3), 92.3 (C), 103.5 (CH), 110.2 (C), 114.3 (CH), 116.7 (C), 120.9 (CH), 126.1 (CH), 127.5 (CH), 127.8 (CH), 128.5 (CH), 131.8 (CH), 132.0, 132.6 (CH), 132.9 (C), 135.3 (C), 139.9, 141.8 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3364 (w), 3128 (w), 3060 (w), 3023 (w), 2954 (w), 2920 (w), 2855 (w), 2223 (s), 1898 (w), 1762 (w), 1682 (m), 1581 (s), 1565 (s), 1514 (s), 1487 (s), 1449 (s), 1440 (s), 1382 (s), 1358 (m), 1299 (s), 1261 (m), 1237 (m), 1218 (m), 1204 (m), 1181 (m), 1149 (m),

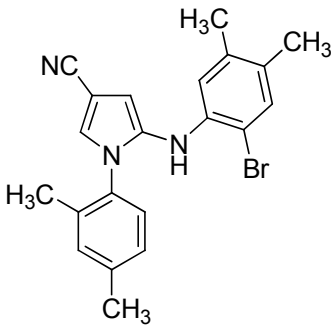
1127 (m), 1118 (m), 1105 (m), 1042 (m), 1021 (s), 979 (m), 930 (w), 876 (w), 817 (s), 801 (s), 773 (m), 742 (s), 693 (m), 653 (m), 635 (s), 598 (m), 579 (m), 549 (m);

MS (GC, 70 eV) *m/z* (%): 368 (21), 367 ([M]$^+$, ^{81}Br, 99), 366 (26), 365 ([M]$^+$, ^{79}Br, 100), 286 ([M-Br]$^+$, 22), 271 (18), 270 (12), 180 (12), 155 (15), 103 (10), 77 (21);

HRMS (EI): calcd. for $C_{19}H_{16}BrN_3$ ([M]$^+$, ^{79}Br) 365.05221, found 365.05212;

HRMS (EI): calcd. for $C_{19}H_{16}BrN_3$ ([M]$^+$, ^{81}Br) 367.05017, found 367.05033.

5-(2-bromo-4,5-dimethylphenylamino)-1-(2,4-dimethylphenyl)-1*H*-pyrrole-3-carbonitrile (16c):



Starting with **15** (100 mg, 0.47 mmol), bromoarene (137 mg, 1.1 equiv.), $Pd(OAc)_2$ (5.3 mg, 5 mol. %), DPEphos (25.4 mg, 10 mol. %), Cs_2CO_3 (385 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16c** was isolated as a brown solid (103 mg, 55 %). mp = 124-125 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 5.44 (s, 1H, N*H*), 6.29 (d, ^4J = 1.7 Hz, 1H, CH_{Ar}), 6.75 (s, 1H, CH_{Ar}), 7.0 – 7.07 (m, 3H, CH_{Ar}), 7.12 (m, 2H, CH_{Ar});

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5 (CH_3), 18.7 (CH_3), 19.9 (CH_3), 21.3 (CH_3), 92.2 (C), 102.0 (CH), 107.1 (C), 115.9 (CH), 116.9 (C), 125.7 (CH), 127.6 (CH), 127.8 (CH), 129.6 (C), 132.1 (CH), 132.7 (C), 133.0 (C), 133.0 (CH), 135.4 (C), 137.1 (C), 139.2 (C), 139.8 (C);

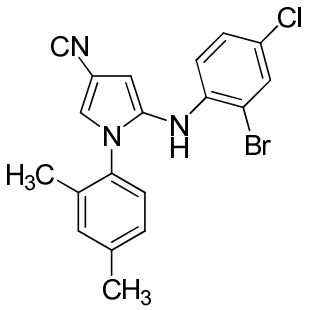
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3355 (w), 3120 (w), 2919 (w), 2855 (w), 2217 (s), 1609 (w), 1507 (s), 1514 (s), 1496 (s), 1444 (s), 1389 (s), 1381 (s), 1368 (m), 1286 (m), 1272 (s), 1222 (m), 1193 (w), 1175 (s), 1147 (m), 1127 (m), 1021 (m), 1008 (m), 973 (s), 866 (s), 830 (s), 809 (s), 724 (m), 694 (m), 676 (w), 637 (s), 546 (m), 528 (m), 510 (m), 436 (s), 419 (s);

MS (GC, 70 eV) *m/z* (%): 396 (23), 395 ([M]$^+$, ^{81}Br, 100), 394 (28), 393 ([M]$^+$, ^{79}Br, 99), 314 (25), 299 (21), 298 (14), 208 (10), 103 (15), 77 (18);

HRMS (EI): calcd. for $C_{21}H_{20}BrN_3$ ([M]$^+$, ^{79}Br) 393.08351, found 393.0832;

HRMS (EI): calcd. for $C_{21}H_{20}BrN_3$ ([M]$^+$, ^{81}Br) 395.08147, found 395.08211.

5-(2-bromo-4-chlorophenylamino)-1-(2,4-dimethylphenyl)-1*H*-pyrrole-3-carbonitrile (16d):



Starting with **15** (100 mg, 0.47 mmol), bromoarene (165 mg, 1.1 equiv.), $Pd(OAc)_2$ (5.3 mg, 5 mol. %), DPEphos (25 mg, 10 mol. %), Cs_2CO_3 (385 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16d** was isolated as a brown solid (133 mg, 70 %). mp = 127-128 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3H CH_3), 2.35 (s, 3H CH_3), 5.57 (s, 1H, N*H*), 6.36 (dd, ^4J = 1.8 Hz, ^4J = 0.7 Hz, 1H, CH_{Ar}), 6.80 (d, ^3J = 8.8 Hz, 1H, CH_{Ar}), 7.00 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.03 (dd, ^3J = 8.1 Hz, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.07-7.13 (m, 3H, CH_{Ar}), 7.35 (d, ^4J = 2.3 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.5 (CH_3), 21.3 (CH_3), 92.5 (C), 104.3 (CH), 110.0 (C), 114.7 (CH), 116.5 (C), 124.7, 126.5 (CH), 127.5 (CH), 127.8 (CH), 128.5 (CH), 131.2 (C), 132.0 (CH), 132.1 (CH), 132.8 (C), 135.2 (C), 140.0 (C), 140.8 (C);

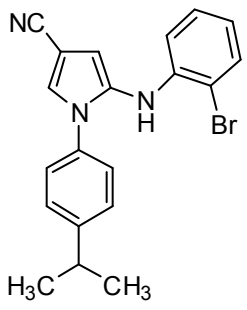
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3393 (w), 3129 (w), 3059 (w), 2921 (w), 2851 (w), 2224 (s), 1685 (w), 1576 (m), 1561 (m), 1513 (s), 1481 (s), 1466 (s), 1384 (s), 1354 (m), 1309 (m), 1296 (s), 1265 (s), 1237 (m), 1220 (m), 1186 (s), 1150 (m), 1127 (m), 1100 (m), 1035 (s), 1004 (w), 980 (w), 927 (w), 869 (m), 836 (m), 818 (s), 798 (s), 782 (s), 721 (m), 692 (m), 664 (m), 640 (s), 601 (s), 567 (m), 544 (s), 464 (m), 432 (m);

MS (GC, 70 eV) *m/z* (%): 403 (26), 402 (23), 401 ($[M]^+$, 100), 400 (20), 399 (74), 320 (16), 285 (12), 195 (13), 77 (16);

HRMS (EI): calcd. for $C_{19}H_{15}BrClN_3$ ($[M]^+$, ^{79}Br) 399.01324, found 399.01292;

HRMS (EI): calcd. for $C_{19}H_{15}BrClN_3$ ($[M]^+$, ^{81}Br, ^{35}Cl) 401.01119, found 401.01103;

5-(2-bromophenylamino)-1-(4-isopropylphenyl)-1*H*-pyrrole-3-carbonitrile (16e):



Starting with **15** (100 mg, 0.44 mmol), bromoarene (115 mg, 1.1 equiv.), $Pd(OAc)_2$ (5 mg, 5 mol. %), DPEphos (24 mg, 10 mol. %), Cs_2CO_3 (361 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16e** was isolated as a brown solid (133 mg, 79 %). mp = 101-102ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, ^3J = 6.9 Hz, 6H), 2.94 (p, ^3J = 6.9 Hz, 1H), 5.74 (s, 1H, N*H*), 6.41 (dd, ^4J = 2.0 Hz, ^4J = 0.9 Hz, 1H,

CH_{Ar}), 6.69 (ddd, ^3J = 7.9 Hz, ^3J = 7.3 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 6.76 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.09 – 7.21 (m, 3H, CH_{Ar}), 7.24 – 7.29 (m, 3H, CH_{Ar}), 7.41 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 24.0 ($CH(CH_3)_2$), 33.9 ($CH(CH_3)_2$), 92.6 (C), 106.8 (CH), 109.8 (C), 114.2 (CH), 116.5 (C), 120.8 (CH), 125.3 (CH), 126.4 (CH), 127.7 (CH), 128.6 (CH), 130.8 (C), 132.7 (CH), 134.5 (C), 142.7 (C), 149.7 (C);

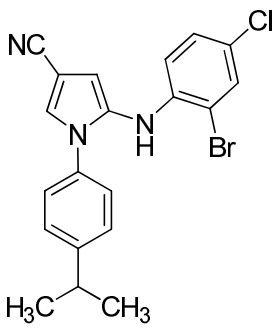
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3328 (w), 3123 (w), 3061 (w), 2956 (w), 2922 (w), 2867 (w), 2221 (s), 1901 (w), 1666 (w), 1607 (w), 1586 (m), 1576 (m), 1563 (w), 1518 (s), 1506 (s), 1488 (s), 1451 (m), 1419 (m), 1393 (m), 1362 (w), 1338 (w), 1301 (m), 1290 (m), 1246 (w), 1226 (w), 1179 (m), 1158 (w), 1149 (w), 1117 (w), 1097 (w), 1055 (w), 1045 (w), 1021 (s), 979 (w), 943 (w), 932 (w), 923 (w), 893 (w), 874 (w), 856 (w), 836 (s), 822 (s), 740 (s), 704 (w), 691 (w), 684 (w), 645 (s), 628 (s), 602 (m), 584 (m), 544 (m);

MS (GC, 70 eV) *m/z* (%): 382 (22), 381 ([M]$^+$, ^{81}Br, 96), 380 (25), 379 ([M]$^+$, ^{79}Br, 100), 366 (18), 364 (18), 285 (10), 284 (12), 258 (22), 257 (27), 155 (15), 103 (12), 77 (17);

HRMS (EI): calcd. for $C_{20}H_{18}BrN_3$ ([M]$^+$, ^{79}Br) 379.06786, found 379.06758;

HRMS (EI): calcd. for $C_{20}H_{18}BrN_3$ ([M]$^+$, ^{81}Br) 381.06582, found 381.06594.

5-(2-bromo-4,5-dimethylphenylamino)-1-(4-isopropylphenyl)-1*H*-pyrrole-3-carbonitrile (16f):



Starting with **15** (100 mg, 0.44 mmol), bromoarene (155 mg, 1.1 equiv.), $Pd(OAc)_2$ (5 mg, 5 mol. %), DPEphos (24 mg, 10 mol. %), Cs_2CO_3 (361 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16f** was isolated as a yellowish oil (133 mg, 72 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, ^3J = 6.9 Hz, 6H, 2*CH_3), 2.92 (p, ^3J = 6.9 Hz, 1H, CH), 5.69 (s, 1H, N*H*), 6.40 (dd, ^4J = 1.9 Hz, ^4J = 0.9 Hz, 1H, CH_{Ar}), 6.64 (d, ^3J = 8.8 Hz, 1H, CH_{Ar}), 7.08 (dd, ^3J = 8.8 Hz, ^4J = 2.3 Hz, 1H, CH_{Ar}), 7.13 (d, ^3J = 8.5 Hz, 2H), 7.2 – 7.3 (m, 3H, CH_{Ar}), 7.39 (d, ^4J = 2.3 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 24.0 ($CH(CH_3)_2$), 33.9 ($CH(CH_3)_2$), 92.7 (C), 107.4 (CH), 109.7 (C), 114.7 (CH), 116.3 (C), 124.6 (C), 125.2 (CH), 126.7 (CH), 127.7 (CH), 128.6 (CH), 130.2 (C), 132.0 (CH), 134.3 (C), 141.7 (C), 149.9 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3368 (w), 3130 (w), 3063 (w), 3039 (w), 2958 (w), 2925 (w), 2868 (w), 2224 (s), 1903 (w), 1764 (w), 1680 (w), 1586 (m), 1572 (m), 1561 (m), 1518 (s), 1481 (s),

1420 (w), 1383 (s), 1361 (m), 1315 (m), 1294 (s), 1263 (m), 1244 (w), 1223 (w), 1204 (w), 1180 (m), 1152 (w), 1140 (w), 1100 (m), 1055 (w), 1032 (s), 1022 (m), 1003 (w), 979 (w), 945 (w), 921 (w), 864 (m), 837 (s), 802 (s), 757 (w), 731 (m), 693 (w), 638 (s), 627 (m), 609 (m), 545 (s);

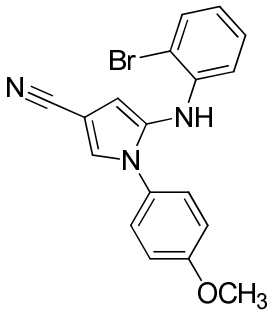
MS (GC, 70 eV) *m/z* (%): 403 (26), 402 (23), 401 ($[M]^+$, 100), 400 (20), 399 (74), 320 (16), 285 (12), 195 (13), 77 (16);

HRMS (EI): calcd. for $C_{20}H_{17}BrClN_3$ ($[M]^+$, ^{79}Br, ^{35}Cl) 413.02889, found 413.02795;

HRMS (EI): calcd. for $C_{20}H_{17}BrClN_3$ ($[M]^+$, ^{79}Br, ^{37}Cl) 415.02594, found 415.02603;

HRMS (EI): calcd. for $C_{20}H_{17}BrClN_3$ ($[M]^+$, ^{81}Br, ^{35}Cl) 417.02389, found 417.02313.

5-(2-bromophenylamino)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbonitrile (16g):



Starting with **15** (100 mg, 0.468 mmol), bromoarene (121 mg, 1.1 equiv.), $Pd(OAc)_2$ (5.2 mg, 5 mol. %), DPEphos (25 mg, 10 mol. %), Cs_2CO_3 (382 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16g** was isolated as a light brown solid (159 mg, 92 %), mp = 125-126 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3H, OCH_3), 5.72 (s, 1H, N*H*), 6.39 (dd, ^4J = 2.0 Hz, ^4J = 0.9 Hz, 1H, CH_{Ar}), 6.61 – 6.77 (m, 2H, CH_{Ar}), 6.90 (d, ^3J = 8.9 Hz, 2H, CH_{Ar}), 7.08 – 7.20 (m, 3H, CH_{Ar}), 7.22 (d, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.39 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar});

^{13}C NMR (75 MHz, $CDCl_3$): δ =55.6 (OCH_3), 92.3 (C), 106.6 (CH), 109.6 (C), 113.9 (CH), 114.7 (CH), 116.4 (C), 120.6 (CH), 126.4 (CH), 126.6 (CH), 128.5 (CH), 129.5 (C), 130.7 (C), 132.6 (CH), 142.5 (C), 159.6 (C);

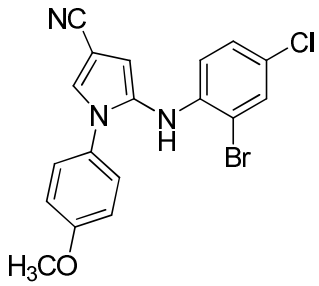
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3387 (w), 3321 (w), 3126 (w), 3066 (w), 3015 (w), 2961 (w), 2929 (w), 2835 (w), 2227 (s), 1888 (w), 1681 (w), 1609 (w), 1587 (s), 1575 (s), 1562 (s), 1518 (s), 1485 (s), 1452 (s), 1411 (m), 1397 (m), 1357 (w), 1316 (w), 1299 (s), 1291 (s), 1251 (s), 1222 (m), 1178 (s), 1170 (s), 1152 (m), 1107 (m), 1022 (s), 979 (m), 931 (w), 859 (w), 834 (s), 802 (s), 795 (s), 748 (s), 742 (s), 722 (m), 688 (m), 650 (m), 628 (s), 616 (s), 601 (s), 585 (s), 557 (s), 530 (s);

MS (EI, 70eV): *m/z* (%) = 370 ([M+H]$^+$, ^{81}Br, 20), 369 ([M]$^+$, ^{81}Br, 98), 368 ([M+H]$^+$, ^{79}Br, 25), 367 ([M]$^+$, ^{79}Br, 100), 354 (23), 352 (24), 288 (22), 272 (13), 244 (16), 155 (13), 138 (11), 77 (13), 76 (11);

HRMS (EI): calcd. for $C_{18}H_{14}BrN_3O$ ([M]$^+$, ^{79}Br) 367.03148, found 367.03086;

HRMS (EI): calcd. for $C_{18}H_{14}BrN_3O$ ([M]$^+$, ^{81}Br) 369.02943, found 369.02906.

5-(2-bromo-4-chlorophenylamino)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbonitrile (16h):



Starting with **15** (100 mg, 0.468 mmol), bromoarene (163 mg, 1.1 equiv.), $Pd(OAc)_2$ (5.2 mg, 5 mol. %), DPEphos (25.2 mg, 10 mol. %), Cs_2CO_3 (382 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16h** was isolated as a yellowish oil (119 mg, 63 %).

^{1}H NMR (300 MHz, CDCl3): δ = 3.80 (s, 3H, OCH_3), 5.70 (s, 1H, N*H*), 6.38 (dd, ^4J = 1.9 Hz, ^4J = 0.9 Hz, 1H, CH_{Ar}), 6.60 (d, ^3J = 8.8 Hz, 1H, CH_{Ar}), 6.89 (d, ^3J = 8.9 Hz, 2H, CH_{Ar}), 7.07 (dd, ^3J = 8.9 Hz, ^4J = 2.3 Hz, 1H, CH_{Ar}), 7.13 (d, ^3J = 9.0 Hz, 2H, CH_{Ar}), 7.23 (d, ^4J = 2.0 Hz, 1H, CH_{Ar}), 7.38 (d, ^4J = 2.3 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 55.55 (OCH_3), 92.3 (C), 107.1 (CH), 109.4 (C), 114.4 (CH), 114.7 (CH), 116.2 (C), 124.4 (C), 126.5 (CH), 126.8 (CH), 128.4 (CH), 129.3 (C), 130.1 (C), 131.9 (CH), 141.5 (C), 159.6 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3355 (w), 3123 (w), 3073 (w), 3058 (w), 2966 (w), 2914 (w), 2835 (w), 2222 (s), 1875 (w), 1678 (w), 1608 (w), 1589 (m), 1574 (m), 1561 (m), 1517 (s), 1506 (s), 1490 (s), 1467 (s), 1438 (m), 1395 (m), 1385 (m), 1362 (m), 1300 (s), 1284 (m), 1245 (s), 1223 (m), 1180 (m), 1170 (s), 1159 (m), 1138 (m), 1118 (m), 1107 (m), 1030 (s), 979 (m), 949 (w), 872 (w), 852 (m), 832 (s), 806 (s), 765 (m), 730 (s), 719 (m), 690 (m), 651 (m), 645 (m), 624 (s), 604 (m), 563 (m), 532 (s);

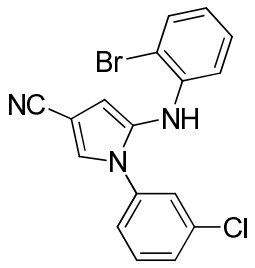
MS (EI, 70eV): *m/z* (%) = 405 (27), 404 ([M+H]$^+$, ^{81}Br, 21), 403 ([M]$^+$, ^{81}Br, 100), 402 ([M+H]$^+$, ^{79}Br, 19), 401 ([M]$^+$, ^{79}Br, 80), 388 (23), 322 (13), 287 (13), 272 (13), 189 (12), 143 (24), 134 (23), 108 (24), 92 (16), 77 (19), 64 (17), 63 (10);

HRMS (ESI-TOF): calcd for $C_{18}H_{13}BrClN_3O$ ([M]$^+$, ^{79}Br) 402.00033, found 401.99996;

HRMS (ESI-TOF): calcd for $C_{18}H_{13}BrClN_3O$ ([M]$^+$, ^{81}Br) 403.9982, found 403.99775.

5-(2-bromophenylamino)-1-(3-chlorophenyl)-1*H*-pyrrole-3-carbonitrile (16i):

Starting with **15** (100 mg, 0.46 mmol), bromoarene (119 mg, 1.1 equiv.), $Pd(OAc)_2$ (5 mg, 5 mol. %), DPEphos (24.7 mg, 10 mol. %), Cs_2CO_3 (374 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16i** was isolated as a brown solid (128 mg, 75 %), mp = 145-146 ºC;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.7 (s, 1H, N*H*), 6.4 (dd, ^4J = 1.8 Hz, ^4J = 0.9 Hz, 1H, CH_{Ar}), 6.6 – 6.77 (m, 2H, CH_{Ar}), 7.08 – 7.13 (m, 1H, CH_{Ar}), 7.13 – 7.18 (m, 1H, CH_{Ar}), 7.28 – 7.31 (m, 2H, CH_{Ar}), 7.36 – 7.32 (m, 2H, CH_{Ar}), 7.41 (dd, ^3J = 7.9 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 93.5 (C), 108.1 (CH), 109.8 (C), 114.1 (CH), 116.0 (C), 121.1 (CH), 123.4 (CH), 125.6 (CH), 126.3 (CH), 128.6 (CH), 128.9 (CH), 130.6 (C), 130.6 (CH), 132.8 (CH), 135.3 (C), 137.8 (C), 142.5 (C).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3339.1 (s), 3130.3 (w), 3087.5 (w), 3019.1 (w), 2956.2 (w), 2921.6 (w), 2851.5 (w), 2221.7 (s), 1591.5 (m), 1575.6 (m), 1511.4 (m), 1488.1 (m), 1476.7 (m), 1449.1 (m), 1434.1 (m), 1416.2 (m), 1388 (m), 1355.4 (w), 1293.9 (m), 1264.3 (w), 1182.5 (m), 1154.6 (w), 1119 (w), 1095.8 (w), 1021.7 (m), 816.5 (m), 743.6 (s), 680.7 (m), 632.3 (m).

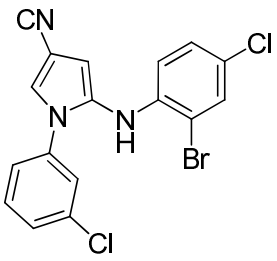
MS (EI, 70eV): *m/z* (%) = 375 ($[M]^+$, ^{81}Br, ^{37}Cl, 28), 374 ($[M-1]^+$, ^{81}Br, ^{37}Cl, 22), 373 ($[M]^+$, ^{81}Br, 100), 372 ($[M]^+$, ^{79}Br, ^{37}Cl, 19), 371 ($[M]^+$, ^{79}Br, ^{35}Cl, 80), 294 (10), 292 (28), 291 (10), 258 (10), 257 (52), 256 (21), 229 (10), 181 (13), 155 (26), 138 (11), 77 (11), 76 (15), 75 (26).

HRMS (EI) calcd for $C_{17}H_{11}N_3BrCl$ ($[M]^+$) 370.98194, found 370.98148;

HRMS (EI) calcd for $C_{17}H_{11}N_3Br^{37}Cl$ ($[M]^+$) 372.97899, found 372.97931;

HRMS (EI) calcd for $C_{17}H_{11}N_3{}^{81}Br^{37}Cl$ ($[M]^+$) 374.97694, found 374.97714.

5-(2-bromo-4-chlorophenylamino)-1-(3-chlorophenyl)-1*H*-pyrrole-3-carbonitrile (16j):



Starting with **15** (100 mg, 1.0 mmol), bromoarene (160 mg, 1.1 equiv.), $Pd(OAc)_2$ (5.1 mg, 5 mol. %), DPEphos (24.7 mg, 10 mol. %), Cs_2CO_3 (374 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16j** was isolated as a yellowish solid (118 mg, 63 %). mp = 161-162 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.71 (s, 1H, N*H*), 6.44 (dd, ^4J = 1.9 Hz, ^4J = 1.0 Hz, 1H, CH_{Ar}), 6.55 (d, ^3J = 8.7 Hz, 1H, CH_{Ar}), 7.08 (dd, ^3J = 8.8 Hz, ^4J = 2.3 Hz, 1H, CH_{Ar}), 7.13 (dt, ^3J = 6.6 Hz, ^4J = 2.2 Hz, 1H, CH_{Ar}), 7.27 – 7.30 (m, 2H, CH_{Ar}), 7.33 – 7.37 (m, 2H, CH_{Ar}), 7.40 (d, ^4J = 2.3 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 93.6 (C), 108.5 (CH), 109.7 (C), 114.6 (CH), 115.8 (C), 123.4 (CH), 125.0 (C), 125.6 (CH), 126.5 (CH), 128.7 (CH), 129.1 (CH), 130.1 (C), 130.7 (CH), 132.1 (CH), 135.4 (C), 137.6 (C), 141.4 (C);

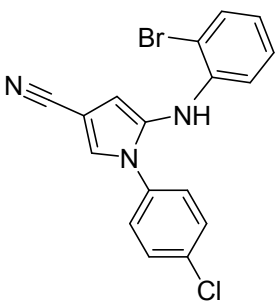
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3381 (w), 3144 (w), 3065 (w), 2922 (w), 2226 (s), 1598 (m), 1587 (m), 1528 (m), 1478 (s), 1458 (s), 1424 (m), 1396 (s), 1371 (m), 1351 (m), 1317 (s), 1240 (w), 1221 (m), 1160 (s), 1095 (s), 1079 (m), 1032 (m), 1020 (m), 998 (w), 981 (w), 914 (w), 889 (m), 857 (s), 793 (s), 776 (s), 739 (s), 711 (s), 695 (s), 683 (s), 656 (m), 633 (m), 615 (s), 538 (s), 502 (m), 488 (s), 452 (s), 442 (s), 414 (s);

MS (GC, 70 eV) *m/z* (%): 409 (48), 408 (21), 407 (100), 406 (16), 405 (65), 293 (17), 292 (13), 291 (49), 290 (13), 256 (11), 189 (12), 138 (12), 111 (23), 75 (23);

HRMS (EI): calcd. for $C_{17}H_{10}BrCl_2N_3$ ($[M]^+$, ^{81}Br, ^{35}Cl) 406.94092, found 406.94079;

HRMS (EI): calcd. for $C_{19}H_{15}BrClN_3$ ($[M]^+$, ^{81}Br, ^{35}Cl, ^{37}Cl) 408.93797, found 408.93854.

5-(2-bromophenylamino)-1-(4-chlorophenyl)-1*H*-pyrrole-3-carbonitrile (16k):



Starting with **15** (100 mg, 0.46 mmol), bromoarene (119 mg, 1.1 equiv.), $Pd(OAc)_2$ (5.1 mg, 5 mol. %), DPEphos (24.7 mg, 10 mol. %), Cs_2CO_3 (374 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16k** was isolated as a white solid (120 mg, 70 %), mp = 118-120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.71 (s, 1H, N*H*), 6.44 (dd, ^4J = 2.0 Hz, ^4J = 1.0 Hz, 1H, CH_{Ar}), 6.64 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 6.7 (ddd, ^3J = 8.0 Hz, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.11 (ddd, ^3J = 8.5 Hz, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.20 (d, ^3J = 8.7 Hz, 2H, CH_{Ar}), 7.27 (d, ^4J = 2.0 Hz, 1H, CH_{Ar}), 7.38 (d, ^3J = 8.8 Hz, 2H), 7.41 (dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar});

^{13}C NMR (75 MHz, $CDCl_3$): δ = 93.4 (C), 108.1 (CH), 109.7 (C), 114.0 (CH), 116.0 (C), 121.0 (CH), 126.3 (CH), 126.5 (CH), 128.7 (CH), 129.9 (CH), 130.6 (C), 132.8 (CH), 134.7 (C), 135.3 (C), 142.6 (C);

IR (ATR, cm^{-1}): = 3384.5 (m), 3138.5 (w), 3111.4 (w), 2960.7 (w), 2919.1 (w), 2849.8 (w), 2226.6 (s), 1585.1 (m), 1565.5 (m), 1514.7 (m), 1489.9 (s), 1452.6 (m), 1424.6 (m), 1407.5 (m), 1387.2 (w), 1359.3 (w), 1301.9 (m), 1292.5 (m), 1260.7 (w),

1151 (w), 1093.2 (m), 1023.2 (m), 1018.2 (m), 930.9 (w), 832.3 (m), 804.2 (m), 740 (s), 638 (m), 608.4 (m).

MS (EI, 70eV): *m/z* (%) = 375 (24), 374 (20), 373 ($[M]^+$, 100), 372 (19), 371 (74), 292 (27), 257 (47), 256 (20), 181 (10), 155 (23), 138 (12), 111 (21), 77 (10), 76 (14), 75 (24).

HRMS (EI) calcd for $C_{17}H_{11}N_3BrCl$ ($[M]^+$) 370.98194, found 370.98136;

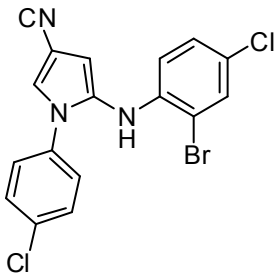
HRMS (EI) calcd for $C_{17}H_{11}N_3Br^{37}Cl$ ($[M]^+$) 372.97939, found 372.97899;

HRMS (EI) calcd for $C_{17}H_{11}N_3{}^{81}BrCl$ ($[M]^+$) 372.97939, found 372.97989;

HRMS (EI) calcd for $C_{17}H_{11}N_3{}^{81}Br^{37}Cl$ ($[M]^+$) 374.97694, found 374.97792.

5-(2-bromo-4-chlorophenylamino)-1-(4-chlorophenyl)-1*H*-pyrrole-3-carbonitrile (16l):

Starting with **15** (100 mg, 1.0 mmol), bromoarene (160 mg, 1.1 equiv.), $Pd(OAc)_2$ (5.1 mg, 5 mol. %), DPEphos (24.7 mg, 10 mol. %), Cs_2CO_3 (374 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16l** was isolated as a brownish solid (140 mg, 75 %), mp = 93-94 ºC;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.67 (s, 1H, N*H*), 6.41 – 6.47 (m, 1H, CH_{Ar}), 6.54 (d, ^3J = 8.7 Hz, 1H, CH_{Ar}), 7.08 (dd, ^3J = 8.7 Hz, ^4J = 2.4 Hz, 1H, CH_{Ar}), 7.18 (d, ^3J = 8.7 Hz, 2H, CH_{Ar}), 7.27 (d, ^4J = 2.0 Hz, 1H, CH_{Ar}), 7.39 (d, ^3J = 8.8 Hz, 2H, CH_{Ar}), 7.4 (d, ^4J = 2.4 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 93.5 (C), 108.5 (CH), 109.6 (C), 114.5 (CH), 115.9 (C), 125.0 (C), 126.5 (CH), 126.6 (CH), 128.7 (CH), 130.0 (CH), 130.03 (C), 132.2 (CH), 134.9 (C), 135.2 (C), 141.5 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3388 (w), 3130 (w), 2922 (w), 2852 (w), 2227 (s), 1676 (w), 1586 (w), 1570 (w), 1558 (w), 1511 (s), 1491 (s), 1480 (s), 1472 (s), 1392 (s), 1381 (s), 1352 (m), 1312 (m), 1288 (s), 1267 (s), 1220 (w), 1178 (s), 1143 (m), 1092 (s), 1031 (s), 1020 (s), 1001 (w), 978 (w), 859 (s), 832 (s), 817 (s), 801 (s), 785 (s), 732 (m), 708 (m), 665 (m), 639 (s), 601 (m), 588 (w), 542 (m), 530 (s), 490 (s), 459 (s), 434 (m), 419 (s);

MS (EI, 70eV): *m/z* (%) = 409 ($[M]^+$, ^{81}Br, ^{37}Cl, 44), 407 ($[M]^+$, ^{81}Br, ^{35}Cl, 100), 406 (15), 405 (60), 326 (11), 293 (15), 292 (13), 291 (45), 290 (14), 256 (11), 189 (13), 138 (13), 111 (25), 75 (26);

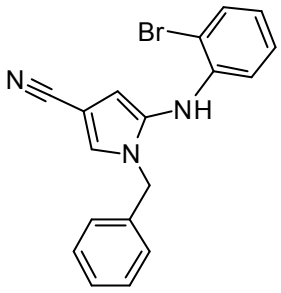
HRMS (EI): calcd. for $C_{17}H_{10}BrCl_2N_3$ ($[M]^+$, ^{81}Br, ^{35}Cl) 406.94092, found 406.94116;

HRMS (EI): calcd. for $C_{17}H_{10}BrCl_2N_3$ ($[M]^+$, ^{79}Br, ^{35}Cl, ^{37}Cl) 406.94002, found 406.94116;

HRMS (EI): calcd. for $C_{17}H_{10}BrCl_2N_3$ ($[M]^+$, ^{81}Br, ^{35}Cl, ^{37}Cl) 408.93797, found 408.93889;

HRMS (EI): calcd. for $C_{17}H_{10}BrCl_2N_3$ ($[M]^+$, ^{81}Br, ^{37}Cl) 408.93707, found 408.93889.

1-benzyl-5-(2-bromophenylamino)-1*H*-pyrrole-3-carbonitrile (16m):



Starting with **15** (100 mg, 0.5 mmol), bromoarene (131 mg, 1.1 equiv.), $Pd(OAc)_2$ (5.6 mg, 5 mol. %), DPEphos (27.3 mg, 10 mol. %), Cs_2CO_3 (412 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16m** was isolated as a yellowish oil (107 mg, 60 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.91 (s, 2H, CH_2), 5.58 (s, 1H, N*H*), 6.33 (dd, ^4J = 1.9 Hz, ^4J = 1.0 Hz, 1H, CH_{Ar}), 6.47 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 6.70 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.05–7.13 (m, 3H, CH_{Ar}), 7.15 (d, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.29 – 7.37 (m, 3H, CH_{Ar}), 7.46 (dd, ^3J = 7.9 Hz, ^3J = 1.5 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 50.3 (CH_2), 91.9 (C), 108.4 (CH), 109.5 (C), 113.8 (CH), 116.6, 120.8 (CH), 126.3 (CH), 127.6 (CH), 128.5 (CH), 128.7 (CH), 129.2 (CH), 130.1 (C), 132.8 (CH), 135.7 (C), 143.1 (C);

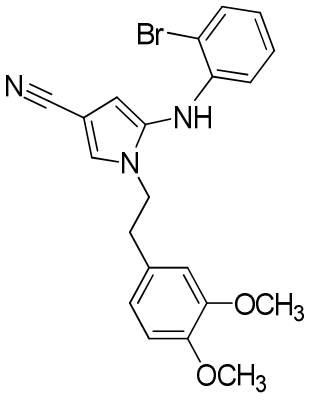
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3369 (w), 3126 (w), 3063 (w), 3029 (w), 2930 (w), 2220 (s), 1677 (w), 1591 (s), 1577 (s), 1563 (s), 1514 (s), 1485 (s), 1451 (s), 1395 (m), 1373 (m), 1346 (m), 1297 (s), 1285 (s), 1238 (m), 1204 (m), 1184 (m), 1076 (w), 1043 (w), 1021 (s), 1003 (w), 978 (m), 930 (w), 866 (w), 804 (m), 743 (s), 719 (s), 695 (s), 632 (s), 587 (m), 567 (m), 541 (m);

MS (EI, 70eV): *m/z* (%) = 353 ($[M]^+$, ^{81}Br, 33), 351 ($[M]^+$, ^{79}Br, 34), 181 (45), 91 (100), 65 (13);

HRMS (EI): calcd. for $C_{18}H_{14}BrN_3$ ($[M]^+$, ^{79}Br) 351.03656, found 351.03583;

HRMS (EI): calcd. for $C_{18}H_{14}BrN_3$ ($[M]^+$, ^{81}Br) 353.03452, found 353.03377.

5-(2-bromophenylamino)-1-(3,4-dimethoxyphenethyl)-1*H*-pyrrole-3-carbonitrile (16n):



Starting with **15** (100 mg, 0.37 mmol), bromoarene (96 mg, 1.1 equiv.), $Pd(OAc)_2$ (4 mg, 5 mol. %), DPEphos (19.8 mg, 10 mol. %), Cs_2CO_3 (300 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16n** was isolated as a yellowish oil (86 mg, 55 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.87 (t, ^3J = 6.7 Hz, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.0 (t, ^3J = 6.7 Hz, 2H, CH_2), 5.10 (s, 1H, N*H*), 6.22 (dd, ^4J = 1.9 Hz, ^4J = 1.0 Hz, 1H, CH_{Ar}), 6.29 – 6.40 (m, 2H, CH_{Ar}), 6.49 (dd, ^3J = 8.1 Hz, ^4J = 2.0 Hz, 1H, CH_{Ar}), 6.67 (td, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 6.8 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.1 (ddd, ^3J = 8.5 Hz, ^3J = 7.4 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.1 (d, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.4 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 37.7 (CH_2), 47.8 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 91.7 (C), 108.1 (CH), 109.1 (C), 111.6 (CH), 111.7 (CH), 113.7 (CH), 116.7, 120.6 (CH), 120.8 (CH), 125.6 (CH), 128.6 (CH), 129.6 (C), 130.2 (C), 132.7 (CH), 143.2 (C), 148.3 (C), 149.2 (C);

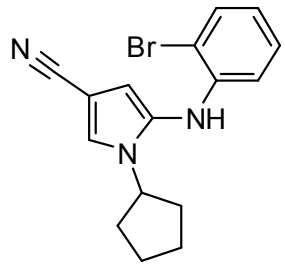
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3359 (w), 3123 (w), 3058 (w), 2997 (w), 2926 (w), 2850 (w), 2833 (w), 2219 (w), 1673 (w), 1589 (m), 1577 (m), 1564 (m), 1513 (s), 1487 (s), 1462 (m), 1448 (s), 1437 (s), 1417 (s), 1397 (m), 1375 (m), 1353 (m), 1298 (m), 1259 (s), 1234 (s), 1186 (m), 1154 (s), 1138 (m), 1122 (s), 1021 (s), 979 (m), 937 (w), 852 (m), 803 (s), 743 (s), 694 (s), 631 (s), 542 (s);

MS (GC, 70 eV) *m/z* (%): 427 ($[M]^+$, ^{81}Br, 38), 425 ($[M]^+$, ^{79}Br, 39), 194 (14), 166 (12), 165 (100), 164 (70), 151 (77), 150 (17), 149 (10), 107 (12), 91 (13), 77 (14);

HRMS (EI): calcd. for $C_{21}H_{20}BrN_3O_2$ ($[M]^+$, ^{79}Br) 425.07334, found 425.07294;

HRMS (EI): calcd. for $C_{21}H_{20}BrN_3O_2$ ($[M]^+$, ^{81}Br) 427.07129, found 427.07155.

5-(2-bromophenylamino)-1-cyclopentyl-1*H*-pyrrole-3-carbonitrile (16o):



Starting with **15** (100 mg, 0.56 mmol), bromoarene (146 mg, 1.1 equiv.), $Pd(OAc)_2$ (6.3 mg, 5 mol. %), DPEphos (30 mg, 10 mol. %), Cs_2CO_3 (460 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16o** was isolated as a white solid (141 mg, 75 %); mp = 109-110 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54 – 1.78 (m, 4H), 1.84 – 1.9 (m, 2H), 2.0 – 2.1 (m, 2H), 4.41 (p, ^3J = 7.1 Hz, 1H, CH_{Ar}), 5.67 (s, 1H, N*H*),

6.28 (dd, ^4J = 2.0 Hz, ^4J = 0.9 Hz, 1H, CH_{Ar}), 6.40 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 6.70 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.11 (ddd, ^3J = 8.5 Hz, ^3J = 7.4 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.19 (d, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.47 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 24.3, 33.9, 56.4, 91.6 (C), 108.4 (CH), 109.3 (C), 113.7 (CH), 116.9, 120.6 (CH), 123.1 (CH), 128.7 (CH), 129.9 (C), 132.7 (CH), 143.7 (C);

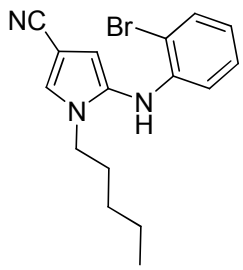
IR (ATR, cm^{-1}): = 3401 (w), 3362 (m), 3116 (w), 3059 (w), 2962 (w), 2870 (w), 2219 (s), 1674 (w), 1592 (m), 1578 (m), 1562 (m), 1513 (m), 1484 (s), 1450 (m), 1373 (m), 1356 (m), 1297 (m), 1197 (m), 1154 (w), 1123 (w), 1045 (w), 1021 (s), 819 (s), 742.5 (s), 639 (s).

MS (EI, 70eV): *m/z* (%) = 332 ([M+H]$^+$, ^{81}Br, 12), 331 (M$^+$, ^{81}Br, 64), 330 ([M+H]$^+$, ^{79}Br, 12), 329 (M$^+$, ^{79}Br, 63), 263 (59), 262 (13), 261 (58), 183 (14), 182 ([M-Br]$^+$, 100), 181 (57), 155 (24), 154 (11), 77 (11), 41 (28);

HRMS (EI) calcd for $C_{16}H_{16}BrN_3$ ([M]$^+$) 329.05221, found 329.05124;

HRMS (EI) calcd for $C_{16}H_{16}{}^{81}BrN_3$ ([M]$^+$) 331.05017, found 331.04950.

5-(2-bromophenylamino)-1-pentyl-1*H*-pyrrole-3-carbonitrile (16p):



Starting with **15** (100 mg, 0.56 mmol), bromoarene (146 mg, 1.1 equiv.), $Pd(OAc)_2$ (6.3 mg, 5 mol. %), DPEphos (30.3 mg, 10 mol. %), Cs_2CO_3 (459 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16p** was isolated as a yellowish oil (141 mg, 76 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.33 – 1.16 (m, 2H, CH_2), 1.67 (p, ^3J = 7.4 Hz, 2H, CH_2), 3.73 (t, ^3J = 7.3 Hz, 2H, CH_2), 5.65 (s, 1H, N*H*), 6.29 (dd, ^4J = 1.9 Hz, ^4J = 0.9 Hz, 1H, CH_{Ar}), 6.42 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 6.71 (ddd, ^3J = 7.9 Hz, ^3J = 7.4 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.06 – 7.20 (m, 2H, CH_{Ar}), 7.47 (dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.95 (CH_3), 22.2 (CH_2), 28.74 (CH_2), 30.6 (CH_2), 46.2 (CH_2), 91.4 (C), 108.3 (CH), 109.45 (C), 113.8 (CH), 116.8 (C), 120.7 (CH), 125.9 (CH), 128.7 (CH), 128.7 (C), 129.8 (C), 132.75 (CH), 133.9 (C), 143.5 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3340 (w), 3126 (w), 3068 (w), 2955 (w), 2928 (m), 2858 (w), 2221 (s), 1721 (w), 1673 (w), 1646 (w), 1619 (w), 1591 (m), 1577 (m), 1563 (m),

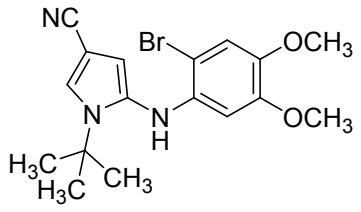
1516 (s), 1487 (s), 1463 (m), 1450 (s), 1397 (m), 1377 (m), 1352 (m), 1297 (s), 1284 (s), 1187 (m), 1157 (w), 1130 (m), 1118 (m), 1073 (w), 1043 (w), 1021 (s), 979 (w), 931 (w), 864 (w), 802 (m), 742 (s), 706 (w), 633 (s), 537 (w);

MS (EI, 70eV): *m/z* (%) = 333 ($[M]^+$, ^{81}Br, 33), 331 ($[M]^+$, ^{79}Br, 38), 252 (11), 210 (10), 197 (14), 196 (99), 194 (13), 182 (40), 181 (30), 155 (13);

HRMS (EI) calcd for $C_{16}H_{18}BrN_3$ ($[M, ^{79}Br]^+$)331.06786, found 331.06755;

HRMS (EI) calcd for $C_{16}H_{18}BrN_3$ ($[M, ^{81}Br]^+$)333.06575, found 333.06582.

5-(2-bromo-4,5-dimethoxyphenylamino)-1-tert-butyl-1*H*-pyrrole-3-carbonitrile (16q):



Starting with **15** (100 mg, 0.61 mmol), bromoarene (199 mg, 1.1 equiv.), $Pd(OAc)_2$ (6.8 mg, 5 mol. %), DPEphos (33 mg, 10 mol. %), Cs_2CO_3 (499 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16q** was isolated by column chromatography as red crystals (156 mg, 68 %), mp = 133-134 ºC;

^1H NMR (300 MHz, $CDCl_3$): δ = 1.58 (s, 9H, $C(CH_3)_3$), 3.67 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.3 (s, 1H, N*H*), 6.1 (s, 1H, CH_{Ar}), 6.3 (dd, ^4J = 2.1 Hz, ^4J = 1.1 Hz, 1H, CH_{Ar}), 7.0 (s, 1H, CH_{Ar}), 7.2 (d, ^4J = 2.1 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 30.4 ($C(CH_3)_3$), 56.2 (OCH_3), 56.9 (OCH_3), 57.9 ($C(CH_3)_3$), 90.1 (C), 98.5 (C), 99.1 (CH), 110.6 (CH), 116.1 (CH), 117.0 (C), 124.1 (CH), 131.5 (C), 138.0 (C), 143.0 (C), 149.8 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3372 (w), 3334 (w), 3153 (w), 2979 (w), 2957 (w), 2931 (w), 2827 (w), 2214 (s), 1614 (w), 1586 (w), 1563 (w), 1507 (s), 1478 (m), 1462 (m), 1444 (m), 1432 (m), 1396 (m), 1380 (m), 1371 (m), 1365 (m), 1357 (m), 1317 (m), 1275 (m), 1260 (m), 1231 (m), 1205 (s), 1170 (s), 1149 (s), 1089 (m), 1033 (s), 985 (m), 929 (w), 871 (w), 832 (s), 806 (s), 789 (m), 748 (m), 697 (m), 669 (m), 634 (s), 613 (m), 598 (m), 576 (m), 554 (m);

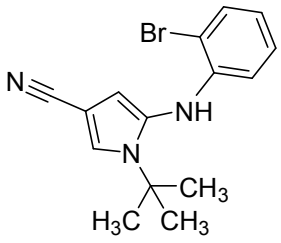
MS (EI, 70 eV) *m/z* (%): 380 (12), 379 (64), 378 (12), 377 $(M]^+$, 64), 324 (16), 323 (100), 322 (16), 321 (95), 308 (40), 306 (38), 243 (11), 242 (59), 241 (18), 226 (26), 211 (29), 198 (11), 184 (12), 183 (10), 57 (28), 29 (11);

HRMS (ESI): calcd for $C_{17}H_{20}N_3O_2$ ($[M]^+$, ^{79}Br) 377.07334, found 377.07283;

HRMS (ESI): calcd for $C_{17}H_{20}N_3O_2$ ($[M]^+$, ^{81}Br) 379.07129, found 379.07124.

5-(2-bromophenylamino)-1-tert-butyl-1*H*-pyrrole-3-carbonitrile (16r):

Starting with **15** (100 mg, 0.61 mmol), bromoarene (159 mg, 1.1 equiv.), $Pd(OAc)_2$ (6.8 mg, 5 mol. %), DPEphos (33 mg, 10 mol. %), Cs_2CO_3 (499 mg, 2.5 equiv.), and 1,4-dioxane (4 mL), **16r** was isolated as a light yellow solid (166 mg, 85 %); mp = 140-141°C.



^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (s, 9H, $C(CH_3)_3$), 5.62 (s, 1H, N*H*), 6.30 (dd, ^4J = 2.0 Hz, ^4J = 1.1 Hz, 1H, CH_{Ar}), 6.50 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 6.68 (ddd, ^3J = 7.9 Hz, ^3J = 7.4 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.05 – 7.15 (m, 1H, CH_{Ar}), 7.24 (d, ^4J = 2.0 Hz, 1H, CH_{Ar}), 7.46 (dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 30.2 ($C(CH_3)_3$), 57.7 ($C(CH_3)_3$), 90.0 (C), 109.34 (C), 111.0 (CH), 114.0 (CH), 116.8 (C), 120.3 (CH), 124.1 (CH), 128.5 (CH), 130.50 (C), 132.5 (CH), 143.7 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3381 (w), 3146 (w), 3104 (w), 3060 (w), 3001 (w), 2799 (w), 3928 (w), 2219 (s), 1589 (m), 1560 (m), 1510 (m), 1488 (m), 1450 (m), 1415 (m), 1337 (m), 1352 (m), 1314 (m), 1299.2 (m), 1207 (m), 1198 (m), 1157 (m), 1085 (m), 1019.3 (m), 838 (m), 828.5 (m), 745 (s), 637 (s).

MS (EI, 70eV): *m/z* (%) = 319 ($[M]^+$, ^{81}Br, 38), 317 ($[M]^+$, ^{79}Br, 38), 264 (13), 263 (97), 261 (100), 183 (12), 182 (82), 181 (58), 155 (26), 154 (11), 76 (11), 57 (32), 41 (23).

HRMS (EI) calcd for $C_{15}H_{16}N_3Br$ ($[M]^+$) 317.05221, found 317.05299;

HRMS (EI) calcd for $C_{15}H_{16}N_3\,^{81}Br$ ($[M]^+$) 319.05017, found 319.05095.

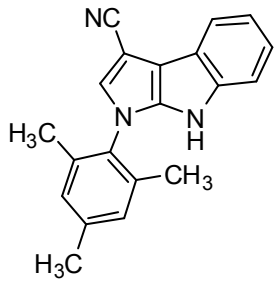
General procedure for the synthesis of compounds 17a-s:

To a Schlenk flask, corresponding compound **16** (100 mg), $Pd(OAc)_2$ (5 mol %), $PCy_3 \cdot HBF_4$ (10 mol %), DBU (2.5 equiv.), and DMA (4-5 mL) were added under an inert atmosphere. The reaction mixture was refluxed at 145 °C for 3-4 h. The solvent was evaporated to dryness and the residue was purified by column chromatography to give compound **16**.

1-mesityl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17a):

Starting from compound **16a** (100 mg, 0.31 mmol), the product **17a** was isolated as yellow solid (68 mg, 71 %); mp = 281-282 °C;

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.97 (s, 6H, CH_3), 2.35 (s, 3H, CH_3), 7.04 – 7.21 (m, 4H, CH_{Ar}), 7.2 – 7.4 (m, 1H, CH_{Ar}), 7.61 (s, 1H, CH_{Ar}), 7.63– 7.75 (m, 1H, CH_{Ar}), 11.48 (s, 1H, N*H*);



^{13}C NMR (63 MHz, DMSO-d_6): δ = 17.0 (CH_3), 20.5 (CH_3), 83.2 (C), 105.7 (C), 112.3 (CH), 117.0, 117.6 (CH), 119.4 (CH), 119.5 (C), 121.3 (CH), 128.8 (CH), 129.0 (CH), 132.5 (C), 135.5 (C), 138.79 (C), 138.81 (C), 139.5 (C);

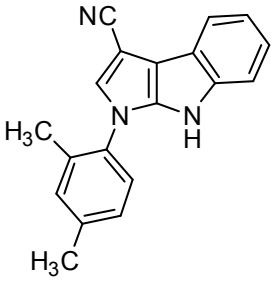
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3240 (w), 3124 (w), 3055 (w), 2953 (w), 2919 (w), 2855 (w), 2223 (m), 1894 (w), 1827 (w), 1781 (w), 1727 (w), 1619 (w), 1577 (m), 1553 (s), 1516 (m), 1490 (m), 1464 (m), 1451 (s), 1376 (w), 1317 (m), 1295 (m), 1261 (m), 1253 (m), 1209 (m), 1176 (m), 1123 (w), 1072 (m), 1047 (m), 989 (m), 957 (m), 913 (w), 883 (w), 851 (m), 835 (m), 767 (s), 737 (s), 710 (s), 700 (m), 662 (m), 637 (m), 603 (s), 594 (s), 548 (s);

MS (GC, 70 eV) *m/z* (%): 300 (20), 299 ([M]$^+$, 100), 298 (35), 284 (27), 247 (23), 232 (11), 231 (11), 91 (15), 77 (14);

HRMS (EI): calcd. for $C_{29}H_{37}N_3$ ([M]$^+$) 299.14170, found 299.14155.

1-(2,4-dimethylphenyl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17b):

Starting from compound **16b** (100 mg, 0.27 mmol), the product **17b** was isolated as yellow solid (66 mg, 85 %); mp = 223-224 ºC;



^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.12 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.09 – 7.20 (m, 2H, CH_{Ar}), 7.23 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H, CH_{Ar}), 7.31 (s, 1H, CH_{Ar}), 7.33 – 7.40 (m, 2H, CH_{Ar}), 7.63 – 7.69 (m, 1H, CH_{Ar}), 7.70 (s, 1H, CH_{Ar}), 11.53 (s, 1H, N*H*);

^{13}C NMR (63 MHz, DMSO-d_6): δ = 17.2 (CH_3), 20.6 (CH_3), 83.3 (C), 105.7 (C), 112.3 (CH), 117.0 (C), 117.6 (CH), 119.4 (CH), 119.5 (C), 121.4 (CH), 126.7 (CH), 127.7 (CH), 129.2 (CH), 131.9 (CH), 133.5 (C), 134.0 (C), 138.8 (C), 139.0 (C), 139.5 (C);

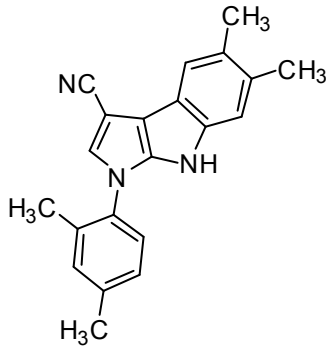
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3286 (w), 3131 (w), 3057 (w), 2919 (w), 2852 (w), 2220 (s), 1621 (w), 1581 (m), 1555 (m), 1520 (m), 1496 (s), 1451 (m), 1375 (w), 1325 (w), 1313 (m), 1251 (m), 1210 (m), 1170 (s), 1133 (m), 1111 (w), 1045 (s), 993 (w), 952

(w), 925 (w), 882 (w), 847 (w), 822 (s), 752 (s), 735 (s), 711 (s), 703 (s), 664 (m), 630 (m), 595 (s), 555 (s), 535 (s), 500 (s), 451 (s), 433 (s);

MS (GC, 70 eV) *m/z* (%): 286 (20), 285 (100), 284 (50), 270 (29), 233 (16);

HRMS (EI): calcd. for $C_{19}H_{15}N_3$ ($[M]^+$) 285.12605, found 285.12596.

1-(2,4-dimethylphenyl)-5,6-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17c):



Starting from compound **16c** (100 mg, 0.25 mmol), the product **17c** was isolated as yellow solid (64 mg, 81 %); mp = 214-216 ºC;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.13 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.06 (s, 1H, CH_{Ar}), 7.09 (s, 1H, CH_{Ar}), 7.14 (dd, ^3J = 7.9 Hz, ^4J = 2.0 Hz, 1H, CH_{Ar}), 7.18 (d, ^4J = 1.8 Hz, 1H, CH_{Ar}), 7.21 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.49 (s, 1H), 7.66 (s, 1H, CH_{Ar});

^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.6 (CH_3), 20.1 (CH_3), 20.6 (CH_3), 21.3 (CH_3), 85.2 (C), 107.9 (C), 112.6 (CH), 117.2 (C), 119.2 (C), 119.8 (CH), 126.6 (CH), 127.4 (CH), 128.1 (CH), 129.4 (C), 131.3 (C), 132.5 (CH), 133.6 (C), 134.5 (C), 138.3 (C), 138.3 (C), 139.7 (C);

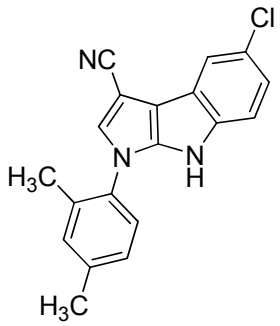
IR (ATR, cm^{-1}): $\tilde{\nu}$ =3254 (w), 3150 (w), 3126 (w), 3015 (w), 2957 (w), 2919 (w), 2854 (w), 2222 (s), 1681 (w), 1568 (w), 1544 (m), 1519 (m), 1501 (s), 1456 (s), 1371 (m), 1346 (w), 1324 (m), 1277 (m), 1235 (m), 1211 (m), 1168 (s), 1132 (m), 1115 (m), 1042 (m), 1022 (m), 1001 (m), 953 (m), 866 (m), 853 (s), 812 (s), 764 (w), 752 (m), 732 (m), 720 (m), 714 (m), 689 (m), 638 (m), 581 (s), 567 (m), 549 (s);

MS (GC, 70 eV) *m/z* (%): 314 (21), 313 ($[M]^+$, 100), 312 (39), 298 (28), 261 (10);

HRMS (EI): calcd. for $C_{21}H_{19}N_3$ ($[M]^+$) 313.15735, found 313.15678.

5-chloro-1-(2,4-dimethylphenyl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17d):

Starting from compound **16d** (100 mg, 0.25 mmol), the product **17d** was isolated as brown solid (60 mg, 75 %); mp = 246-247 °C.



^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.99 – 7.42 (m, 6H, CH_{Ar}). 7.69-7.71 (m, 1H, CH_{Ar}), 10.63 (s, 1H, N*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.4 (CH_3), 20.9 (CH_3), 84.7 (C), 106.2 (C), 113.0 (CH), 116.5 (C), 118.0 (CH), 120.9 (C), 121.4 (CH), 124.8 (C), 126.6 (CH), 127.6 (CH), 128.0 (CH), 131.9 (CH), 133.5 (C), 134.4 (C), 138.0 (C), 139.1 (C), 139.7 (C);

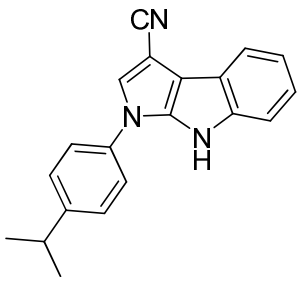
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3259 (w), 3131 (w), 2850 (w), 2223 (s), 1617 (w), 1576 (s), 1558 (w), 1521 (s), 1498 (s), 1441 (s), 1377 (w), 1325 (w), 1285 (m), 1248 (m), 1240 (m), 1206 (m), 1171 (s), 1137 (w), 1070 (m), 1043 (s), 864 (s), 837 (m), 824 (s), 799 (s), 745 (s), 732 (s), 713 (m), 679 (w), 657 (w), 591 (s), 579 (s), 526 (s), 510 (s), 449 (s), 431 (s), 424 (m), 408 (m);

MS (GC, 70 eV) *m/z* (%): 321 (31), 320 (32), 319 ([M]$^+$) 100), 318 (39), 304 (26), 284 (19), 267 (17);

HRMS (EI): calcd. for $C_{19}H_{14}ClN_3$ ([M]$^+$) 319.08708, found 319.08741.

1-(4-isopropylphenyl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17e):

Starting from compound **16e** (100 mg, 0.26 mmol), the product **17e** was isolated as brown solid (65 mg, 82 %); mp = 221-222 °C;



^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.27 (d, ^3J = 6.9 Hz, 6H, CH(CH_3)$_2$), 3.01 (p, ^3J = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$), 7.1 (td, ^3J = 7.5 Hz, ^4J =1.4 Hz, 1H, CH_{Ar}), 7.2 (td, ^3J = 7.6 Hz, 1.6 Hz, 1H, CH_{Ar}), 7.43 – 7.48 (m, 1H, CH_{Ar}), 7.49 (d, ^3J = 8.5 Hz, 2H, CH_{Ar}), 7.68 (d, ^3J = 8.6 Hz, (2+1) H, CH_{Ar}), 8.02 (s, 1H, CH_{Ar}), 11.79 (s, 1H, N*H*);

^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.8 (CH(*C*H$_3$)$_2$), 33.1 (*C*H(CH$_3$)$_2$), 84.2 (C), 107.1 (C), 112.6 (CH), 116.8 (C), 117.6 (CH), 119.2 (C), 119.7 (CH), 121.3 (CH), 121.8 (CH), 127.0 (CH), 127.9 (CH), 135.0 (C), 137.0 (C), 139.6 (C), 147.6 (C);

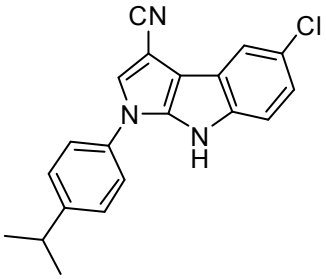
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3253.2 (m), 3146.5 (w), 3056 (w), 2955.8 (m), 2923 (m), 2923 (w), 2863.9 (w), 2224.8 (s), 1909.2 (w), 1871.4 (w), 1835.3 (w), 1794.8 (w), 1755 (w), 1613 (w), 1591 (w), 1544 (m), 1521 (m), 1507 (m), 1451 (m), 1417 (m), 1321(m), 1322 (m), 1258 (m), 1252 (m), 1213 (m), 1176 (m), 1149.9 (m), 1110 (m), 1057.3 (m),

1012.9 (m), 991.8 (m), 918 (m), 818.7 s), 750.9 (m), 736 (s), 721.5 (s), 707.5 (s), 679.8 (m), 613 (m), 577 (m), 536 (s).

MS (EI, 70eV): *m/z* (%) = 300 (21), 299 (100), 284 (35), 257 (19), 256 (51), 127 (17).

HRMS (EI): calcd. for $C_{18}H_{12}ClN_3O$ ($[M]^+$) 321.06634, found 321.06619.

5-chloro-1-(4-isopropylphenyl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17f):



Starting from compound **16f** (100 mg, 0.24 mmol), the product **17f** was isolated as brown solid (63 mg, 80 %); mp = 254-255°C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, ^3J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.93 (p, ^3J = 6.9 Hz, 1H, $CH(CH_3)_2$), 7.05 (dd, ^3J = 8.6 Hz, ^4J = 2.1 Hz, 1H, CH_{Ar}), 7.26 (d, ^3J = 8.6 Hz, 2H), 7.31 (d, ^3J = 8.5 Hz, 2H, CH_{Ar}), 7.43 (d, ^3J = 8.5 Hz, 2H, CH_{Ar}), 7.69 (d, ^4J = 2.1 Hz, 1H, CH_{Ar}), 10.82 (s, 1H, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.9 ($CH(CH_3)_2$), 33.7 ($CH(CH_3)_2$), 85.7 (C), 107.6 (C), 113.2 (CH), 116.5 (C), 118.1 (CH), 120.9, 121.6 (CH), 121.8 (CH), 125.2 (C), 125.95 (CH), 128.0 (CH), 135.2 (C), 138.06 (2*C), 148.4 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3238 (w), 3135 (w), 3080 (w), 3049 (w), 2958 (w), 2935 (w), 2888 (w), 2863 (w), 2230 (s), 1901 (w), 1835 (w), 1709 (w), 1693 (w), 1618 (w), 1590 (w), 1575 (m), 1550 (m), 1520 (s), 1510 (s), 1441 (m), 1427 (m), 1405 (w), 1380 (w), 1361 (w), 1332 (w), 1309 (w), 1287 (m), 1251 (m), 1220 (w), 1209 (m), 1169 (s), 1117 (w), 1096 (w), 1069 (w), 1057 (s), 1013 (m), 961 (w), 942 (w), 920 (w), 883 (w), 856 (m), 834 (s), 825 (m), 792 (s), 762 (m), 744 (s), 730 (s), 711 (w), 690 (w), 663 (w), 638 (w), 613 (w), 587 (s), 571 (m), 557 (m);

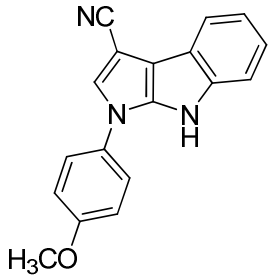
MS (GC, 70 eV) *m/z* (%): 335 ($[M]^+$, ^{37}Cl, 34), 334 (22), 333 ($[M]^+$, ^{35}Cl, 100), 318 (29), 293 (10), 292 (18), 291 (300, 290 (42), 283 (13), 161 (13);

HRMS (EI): calcd. for $C_{20}H_{16}ClN_3$ ($[M]^+$, ^{35}Cl) 333.10273, found 333.10252;

HRMS (EI): calcd. for $C_{19}H_{15}ClN_3$ ($[M]^+$, ^{37}Cl) 335.09978, found 335.09925.

1-(4-methoxyphenyl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17g):

Starting from compound **16g** (100 mg, 0.27 mmol), the product **17g** was isolated as brown solid (47 mg, 60 %); mp = 195-196 °C;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3), 6.98 (d, ^3J = 8.8 Hz, 2H, CH_{Ar}), 7.07 – 7.19 (m, 2H, CH_{Ar}), 7.21-7.26 (m, 1H, CH_{Ar}), 7.33 – 7.40 (m, 1H, CH_{Ar}), 7.44 (d, ^3J = 8.8 Hz, 2H, CH_{Ar}), 7.8 (d, ^3J = 7.1 Hz, 1H, CH_{Ar}), 10.43 (s, 1H, N*H*);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5 (OCH_3), 85.3 (C), 108.1 (C), 112.2 (CH), 115.0 (CH), 116.9 (C), 118.5 (CH), 119.8 (CH), 120.0 (C), 121.8 (CH), 123.1 (CH), 125.5 (CH), 130.6 (C), 137.4 (C), 139.7 (C), 158.6 (C);

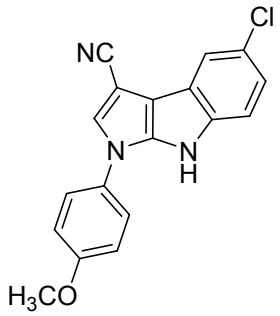
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3257 (w), 3135 (w), 2998 (w), 2958 (w), 2929 (w), 2834 (w), 2754 (w), 2225 (m), 2040 (w), 1619 (w), 1594 (w), 1579 (m), 1553 (m), 1519 (s), 1504 (s), 1451 (s), 1440 (m), 1420 (m), 1379 (w), 1322 (m), 1307 (w), 1296 (m), 1249 (s), 1211 (m), 1172 (s), 1111 (m), 1056 (m), 1033 (s), 1008 (m), 990 (m), 954 (m), 921 (m), 885 (w), 834 (s), 813 (m), 790 (m), 750 (s), 743 (s), 732 (s), 721 (s), 703 (s), 677 (w), 643 (w), 625 (w), 597 (s), 581 (s), 546 (s), 531 (s);

MS (GC, 70 eV) *m/z* (%): 288 ($[M+H]^+$, 20), 287 ($[M]^+$, 100), 286 (19), 273 (12), 272 (64), 244 (31), 243 (19), 154 (10), 127 (18);

HRMS (EI): calcd. for $C_{18}H_{13}N_3O$ ($[M]^+$) 287.10531, found 287.10513.

5-chloro-1-(4-methoxyphenyl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17h):

Starting from compound **16h** (100 mg, 0.25 mmol), the product **17h** was isolated as brown solid (69 mg, 87 %); mp = 263-265 ºC;



^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3), 7.00 (d, ^3J = 8.9 Hz, 2H, CH_{Ar}), 7.05 (dd, ^3J = 8.6 Hz, ^4J = 2.0 Hz, 1H, CH_{Ar}), 7.36 (s, 1H, CH_{Ar}), 7.47 (d, ^3J = 8.9 Hz, 2H, CH_{Ar}), 7.58 (s, 1H, CH_{Ar}), 7.62 (d, ^4J = 1.9 Hz, 1H, CH_{Ar}), 11.34 (s, 1H, N*H*);

^{13}C NMR (63 MHz, $CDCl_3$): δ = 54.9 (OCH_3), 84.2 (C), 106.4, 112.7 (CH), 114.3 (CH), 115.8 (C), 116.9 (CH), 120.0 (C), 120.8 (CH), 122.5 (CH), 124.0 (C), 125.7 (CH), 129.6, 137.4 (C), 137.6 (C), 158.0 (C);

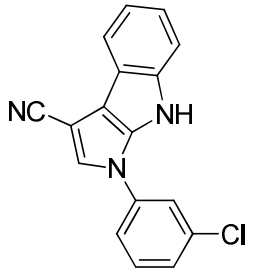
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3229 (w), 3141 (w), 3079 (w), 3014 (w), 3970 (w), 2927 (w), 2835 (w), 2228 (s), 1884 (w), 1854 (w), 1755 (w), 1715 (w), 1621 (w), 1595 (w), 1577 (m), 1551 (w),

1508 (s), 1441 (s), 1302 (w), 1285 (m), 1245 (s), 1209 (m), 1168 (s), 1112 (m), 1068 (w), 1052 (m), 1028 (s), 1005 (m), 952 (w), 933 (w), 885 (w), 858 (m), 831 (s), 813 (m), 802 (s), 753 (s), 742 (m), 725 (s), 686 (w), 662 (w), 637 (w), 614 (m), 589 (s), 563 (s);

MS (GC, 70 eV) *m/z* (%): 323 (33), 322 (29), 321 (100), 320 915), 308 (19), 307 (11), 306 (54), 286 (12), 278 (20), 243 (21), 161 (15);

HRMS (EI): calcd. for $C_{18}H_{12}ClN_3O$ ($[M]^+$) 321.06688, found 321.06693.

1-(3-chlorophenyl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17i):



Starting from compound **16i** (100 mg, 0.27 mmol), the product **17i** was isolated as yellow solid (59 mg, 76 %); mp = 233-235 °C.

^{1}H NMR(300 MHz, DMSO-d_6): δ = 7.17 (td, ^3J = 7.4 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.22 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.45 – 7.56 (m, 2H, CH_{Ar}), 7.64 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.65 – 7.71 (m, 1H, CH_{Ar}), 7.75 – 7.80 (m, 1H, CH_{Ar}), 7.90 (t, ^4J = 2.1 Hz, 1H, CH_{Ar}), 8.14 (s, 1H, CH_{Ar}), 11.95 (s, 1H, N*H*);

^{13}C NMR (63 MHz, DMSO-d_6): δ = 85.2 (C), 107.4 (C), 112.7 (CH), 116.5 (C), 117.7 (CH), 119.0 (C), 119.7 (CH), 119.9 (CH), 121.0 (CH), 122.0 (CH), 127.0 (CH), 127.1 (CH), 131.6 (CH), 134.4 (C), 136.7 (C), 138.3 (C), 139.6 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3242 (w), 3135 (w), 3070 (w), 2922 (w), 2853 (w), 2757 (w), 2224 (s), 1621 (w), 1595 (s), 1585 (s), 1551 (s), 1521 (s), 1508 (m), 1484 (s), 1453 (s), 1434 (m), 1424 (m), 1380 (m), 1333 (m), 1317 (m), 1209 (m), 1170 (m), 1153 (m), 1099 (s), 1078 (m), 1060 (m), 992 (m), 922 (m), 904 (m), 880 (m), 842 (w), 794 (m), 784 (s), 732 (s), 714 (s), 703 (s), 689 (s), 672 (s), 619 (s), 606 (m), 584 (s), 544 (s);

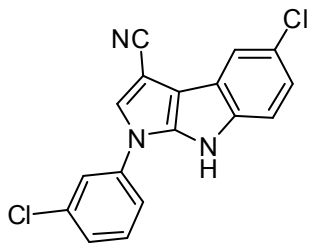
MS (GC, 70 eV) *m/z* (%): 293 (33), 292 (24), 291 (100), 290 (14), 257 (11), 256 (57), 229 (10), 154 (25), 145 (10), 128 (11), 127 (36), 75 (11);

HRMS (ESI-TOF): calcd. for $C_{17}H_{10}ClN_3$ ($[M+H]^+$) 292.0636, found 292.06345;

HRMS (ESI-TOF): calcd. for $C_{17}H_{10}{}^{39}ClN_3$ ($[M+Na]^+$) 316.04308, found 316.04307.

1-(3-chlorophenyl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17j):

Starting from compound **16j** (100 mg, 0.24 mmol), the product **17j** was isolated as yellow solid (58 mg, 72 %); mp = 285-286 °C;



^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.23 (dd, ^3J = 8.7, ^3J = 2.2 Hz, 1H, CH_{Ar}), 7.49 (d, ^3J = 8.7 Hz, 1H, CH_{Ar}), 7.52 (ddd, ^3J = 8.1 Hz, ^4J = 2.0 Hz, ^4J = 1.1 Hz, 1H, CH_{Ar}), 7.62 (d, ^4J = 2.0 Hz, 1H, CH_{Ar}), 7.66 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.74 (ddd, ^3J = 8.1 Hz, ^4J = 2.2 Hz, ^4J = 1.1 Hz, 1H, CH_{Ar}), 7.88 (t, ^4J = 2.1 Hz, 1H, CH_{Ar}), 8.17 (s, 1H, CH_{Ar}), 12.15 (s, 1H, N*H*);

^{13}C NMR (75 MHz, DMSO-d_6): δ = 85.1 (C), 106.6 (C), 114.1 (CH), 116.1 (C), 116.9 (CH), 119.9 (CH), 119.9 (C), 121.2 (CH), 121.7 (CH), 124.2 (C), 127.2 (CH), 128.1 (CH), 131.6 (CH), 134.4 (C), 137.6 (C), 138.0 (C), 138.0 (C);

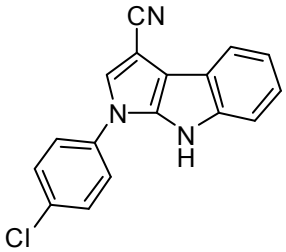
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3216 (w), 3136 (w), 2919 (w), 2234 (m), 1622 (w), 1593 (s), 1586 (m), 1574 (m), 1548 (m), 1507 (s), 1483 (m), 1444 (m), 1407 (w), 1328 (w), 1291 (m), 1273 (w), 1251 (w), 1208 (m), 1188 (w), 1168 (s), 1095 (m), 1071 (w), 1053 (s), 997 (w), 905 (m), 874 (m), 863 (m), 844 (m), 802 (s), 783 (s), 761 (s), 746 (s), 732 (s), 713 (w), 699 (s), 676 (m), 662 (m), 605 (w), 593 (s), 536 (s), 501 (s), 443 (s), 432 (m);

MS (EI, 70eV): *m/z* (%) = 329 (11), 328 (13), 327 (66), 325 (100), 324 (110), 292 (19), 291 (13), 290 (61), 188 (18), 161 (19), 111 (11), 75 (18);

HRMS (EI) calcd for $C_{17}H_9N_3Cl_2$ ($[M]^+$) 325.01680, found 325.01651;

HRMS (EI) calcd for $C_{17}H_9N_3Cl^{37}Cl$ ($[M]^+$) 327.01385, found 327.01398.

1-(4-chlorophenyl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17k):



Starting from compound **16k** (100 mg, 0.27 mmol), the product **17k** was isolated as yellow solid (55 mg, 70 %); mp = 259-260 ºC;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.16 (td, ^3J = 7.5 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 7.22 (td, ^3J = 7.5 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 7.48 (d, ^3J = 7.6 Hz, 1H, CH_{Ar}), 7.68 (d, ^3J = 8.9 Hz, (2+1) H, CH_{Ar}), 7.81 (d, ^3J = 8.9 Hz, 2H, CH_{Ar}), 8.08 (s, 1H, CH_{Ar}), 11.87 (s, 1H, N*H*);

^{13}C NMR (75 MHz, DMSO-d_6): δ = 85.0 (C), 107.4 (C), 112.6 (CH), 116.5 (C), 117.7 (CH), 119.1 (C), 119.9 (CH), 121.9 (CH), 122.9 (C), 127.0 (CH), 129.9 (CH), 131.4 (C), 135.9 (C), 136.8 (C), 139.6 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3290 (w), 3141 (w), 3058 (w), 2957 (w), 2926 (w), 2858 (w), 2753 (w), 2226 (m), 1922 (w), 1877 (w), 1841 (w), 1806 (w), 1723 (w), 1621 (w), 1596 (m), 1587 (w), 1581 (w), 1542 (m), 1518 (s), 1495 (s), 1450 (s), 1431 (m), 1409

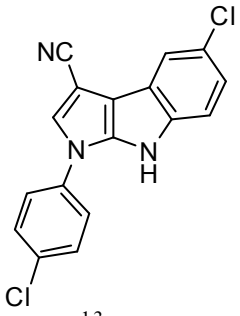
(m), 1377 (m), 1335 (m), 1322 (m), 1278 (m), 1258 (s), 1227 (m), 1210 (m), 1171 (s), 1121 (m), 1094 (s), 1072 (m), 1051 (m), 1012 (m), 992 (m), 965 (w), 926 (w), 918 (w), 886 (w), 825 (s), 811 (s), 749 (s), 743 (s), 726 (s), 707 (s), 700 (s), 678 (m), 651 (w), 638 (w), 621 (m), 605 (m), 577 (s), 535 (m);

MS (GC, 70 eV) *m/z* (%): 293 (34), 292 (25), 291 (100), 290 (16), 257 (14), 256 (68), 229 (10), 154 (22), 146 (11), 127 (35), 126 (10), 75 (17);

HRMS (EI) calcd for $C_{17}H_{10}ClN_3$ ($[M]^+$, ^{35}Cl) 291.05578, found 291.05606;

HRMS (EI) calcd for $C_{17}H_{10}ClN_3$ ($[M]^+$, ^{37}Cl) 293.05283, found 293.05368;

5-chloro-1-(4-chlorophenyl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17l):



Starting from compound **16l** (100 mg, 0.24 mmol), the product **17l** was isolated as yellow solid (45 mg, 56 %); mp = 297-299 ºC;

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.27 (dd, ^3J = 8.7 Hz, ^4J = 1.0 Hz, 1H, CH_{Ar}), 7.53 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 7.7 – 7.8 (m, 1H, CH_{Ar}), 7.74 (d, ^3J = 8.4 Hz, 2H, CH_{Ar}), 7.85 (d, ^3J = 8.7 Hz, 2H, CH_{Ar}), 8.18 (s, 1H, CH_{Ar}), 12.14 (s, 1H, N*H*);

^{13}C NMR (63 MHz, DMSO-d_6): δ = 84.9 (C), 106.6 (C), 114.0 (CH), 116.1 (C), 116.8 (CH), 119.9 (C), 121.6 (CH), 123.0 (CH), 124.1 (C), 127.9 (CH), 129.9 (CH), 131.5 (C), 135.7 (C), 137.7 (C), 138.0 (C);

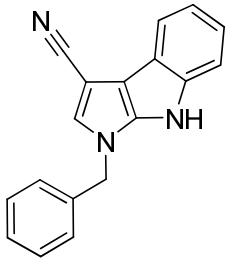
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3233 (w), 3142 (w), 2956 (m), 2924 (m), 2855 (m), 2235 (m), 1884 (w), 1841 (w), 1725 (m), 1645 (w), 1618 (w), 1595 (w), 1587 (w), 1511 (s), 1490 (s), 1451 (m), 1441 (m), 1398 (w), 1378 (w), 1332 (w), 1285 (s), 1276 (s), 1209 (m), 1171 (m), 1121 (m), 1108 (m), 1091 (s), 1069 (s), 1046 (m), 1010 (m), 952 (w), 885 (m), 854 (m), 824 (s), 794 (s), 746 (s), 737 (s), 721 (m), 708 (m), 661 (m), 588 (s), 545 (s);

MS (GC, 70 eV) *m/z* (%): 328 (13), 327 (66), 326 (27), 325 (100), 292 (35), 291 (16), 290 (84), 254 (12), 214 (11), 188 (24), 187 (13), 163 (14), 161 (29), 152 (15), 151 (15), 137 (11), 125 (13), 124 (25), 113 (15), 111 (36), 102 (11), 100 (13), 99 (17), 85 (13), 76 (18), 75 (76), 74 (26), 51 (13), 50 (28);

HRMS (EI) calcd for $C_{17}H_9Cl_2N_3$ ($[M]^+$, ^{35}Cl) 325.01680, found 325.01622;

HRMS (EI) calcd for $C_{17}H_{10}ClN_3$ ($[M]^+$, ^{37}Cl) 327.01385, found 327.01445.

1-benzyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17m):



Starting from compound **16m** (100 mg, 0.28 mmol), the product **17m** was isolated as beige solid (48 mg, 62 %); mp = 181-182 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.22 (s, 2H, CH_2), 7.04 – 7.20 (m, 4H, CH_{Ar}), 7.2 – 7.35 (m, 5H), 7.7 – 7.8 (m, 1H, CH_{Ar}), 10.2 (s, 1H, N*H*);

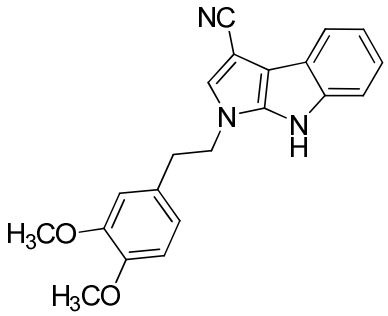
^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.1 (CH_2), 84.0 (C), 107.7 (C), 111.9 (CH), 117.3 (C), 118.6 (CH), 119.7 (CH), 120.4 (C), 121.6 (CH), 126.8 (CH), 127.1 (CH), 128.3 (CH), 129.0 (CH), 135.8 (C), 138.9 (C), 139.7 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3269 (w), 3108 (w), 3062 (w), 3029 (w), 2919 (w), 2850 (w), 2219 (s), 1639 (w), 1621 (w), 1580 (m), 1563 (m), 1521 (m), 1493 (m), 1453 (m), 1317 (m), 1245 (s), 1210 (m), 1174 (m), 1132 (m), 1111 (m), 1077 (m), 1029 (w), 1013 (m), 998 (m), 947 (m), 919 (w), 837 (w), 817 (w), 736 (s), 710 (s), 695 (s), 666 (s), 647 (m), 618 (s), 589 (s), 534 (s), 509 (s), 491 (s), 450 (s), 433 (s);

MS (GC, 70 eV) *m/z* (%): 272 (12), 271 (59), 180 (13), 91 (100), 65 (12);

HRMS (EI) calcd for $C_{18}H_{13}N_3$ ($[M]^+$) 271.11040, found 271.11062;

1-(3,4-dimethoxyphenethyl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17n):



Starting from compound **16n** (100 mg, 0.23 mmol), the product **17n** was isolated as brown solid (49 mg, 60 %); mp = 175-176 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.05 (t, ^{3}J = 6.4 Hz, 2H, CH_2), 3.66 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.23 (t, ^{3}J = 6.4 Hz, 2H, CH_2), 6.43 (d, ^{4}J = 2.0 Hz, 1H, CH_{Ar}), 6.56 (dd, ^{3}J = 8.1 Hz, ^{4}J = 2.0 Hz, 1H, CH_{Ar}), 6.72 (d, ^{3}J = 8.2 Hz, 1H, CH_{Ar}), 6.90 (s, 1H, CH_{Ar}), 7.11 – 7.22 (m, 3H, CH_{Ar}), 7.32 (broad s, 1H, CH_{Ar}/N*H*), 7.75 – 7.80 (m, 1H, CH_{Ar});

^{13}C NMR (75 MHz, $CDCl_3$) δ = 36.6 (CH_2), 50.1 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 83.7 (C), 108.5 (C), 111.6 (CH), 111.8 (CH), 112.0 (CH), 117.1, 118.9 (CH), 120.6 (CH), 120.8, 120.9 (CH), 122.1 (CH), 126.9 (CH), 130.0 (C), 138.2 (C), 139.8 (C), 148.3 (C), 149.2 (C).

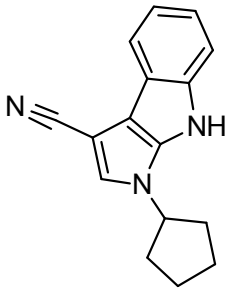
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3253 (w), 3158 (w), 3122 (w), 3064 (w), 2994 (w), 2954 (w), 2929 (w), 2850 (w), 2833 (w), 2219 (s), 1615 (w), 1607 (w), 1582 (m), 1565 (m), 1513 (s), 1492 (m), 1462 (s), 1451 (s), 1440 (m), 1420 (m), 1337 (m), 1320 (m), 1293 (w), 1280 (w), 1259 (s), 1232 (s), 1174 (m), 1144 (s), 1113 (m), 1027 (s), 996 (m), 944

(m), 921 (w), 844 (m), 839 (m), 813 (m), 747 (s), 710 (s), 652 (m), 622 (m), 602 (m), 586 (s), 562 (m), 532 (s);

MS (GC, 70 eV) *m/z* (%): 346 ($[M+H]^+$, 24), 345 ($[M]^+$, 100), 165 (62), 164 (70), 151 (76), 150 (14), 149 (11);

HRMS (ESI-TOF): calcd. for $C_{21}H_{19}N_3O_2$ ($[M+H]^+$) 346.155, found 346.15511.

1-cyclopentyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17o):



Starting from compound **16o** (100 mg, 0.3 mmol), the product **17o** was isolated as beige solid (49 mg, 65 %); mp = 225-226 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 – 1.78 (m, 2H), 1.81 – 2.01 (m, 4H), 2.10 – 2.28 (m, 2H), 4.55 (p, ^3J = 7.1 Hz, 1H), 6.97 – 7.14 (m, 3H, CH_{Ar}), 7.27 – 7.37 (m, 1H, CH_{Ar}), 7.59 – 7.82 (m, 1H, CH_{Ar}), 10.28 (s, 1H, CH_{Ar});

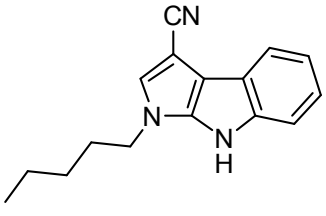
^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.5, 32.1, 58.9, 82.6 (C), 107.45 (C), 111.75 (CH), 117.4 (C), 118.3 (CH), 119.4 (CH), 120.0 (C), 121.2 (CH), 124.3 (CH), 138.2 (C), 139.6 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3260 (w), 3111 (w), 2952 (w), 2923 (w), 2869 (w), 2853 (w), 2220 (m), 1619 (w), 1580 (m), 1558 (m), 1525 (m), 1515 (m), 1491 (m), 1452 (m), 1435 (m), 1395 (m), 1376 (m), 1324 (m), 1295 (w), 1251 (m), 1177 (m), 1144 (m), 1110 (m), 1091 (m), 1035 (m), 1012 (m), 1002 (m), 955 (m), 921 (m), 889 (w), 876 (w), 843 (w), 802 (w), 759 (m), 743 (s), 711 (s), 688 (m), 665 (m), 615 (m), 588 (s), 545 (s);

MS (GC, 70 eV) *m/z* (%): 249 ($[M]^+$, 54), 182 (14), 181 (100), 180 (25), 154 917), 127 (13), 41 (12);

HRMS (EI) calcd for $C_{16}H_{15}N_3$ ($[M]^+$) 249.12605, found 249.12553.

1-pentyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17p):



Starting from compound **16p** (100 mg, 0.3 mmol), the product **17p** was isolated as brown solid (40 mg, 53 %); mp = 171-172 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 6.7 Hz, 3H), 1.23 – 1.43 (m, 4H, 2*CH_2), 1.86 (p, ^3J = 7.1 Hz, 2H, CH_2), 4.03 (t, ^3J = 7.1 Hz, 2H, CH_2), 7.01 (s, 1H, CH_{Ar}), 7.16 – 7.23 (m, 2H, CH_{Ar}), 7.34 – 7.42 (m, 1H, CH_{Ar}), 7.78 – 7.86 (m, 1H, CH_{Ar}), 8.06 (s, 1H, N*H*);

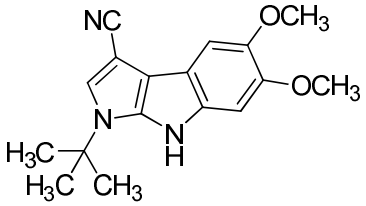
^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.3 (CH_2), 28.9 (CH_2), 29.8 (CH_2), 48.1 (CH_2), 83.7 (C), 108.7 (C), 112.1 (CH), 117.4 (C), 119.1 (CH), 120.7 (CH), 121.0 (C), 122.2 (CH), 127.0 (CH), 138.0 (C), 139.7 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3268 (w), 3124 (w), 3058 (w), 2951 (w), 2923 (w), 2867 (w), 2851 (w), 2214 (s), 1921 (w), 1882 (w), 1845 (w), 1619 (w), 1580 (m), 1563 (m), 1520 (m), 1491 (s), 1452 (m), 1397 (w), 1357 (w), 1318 (m), 1247 (m), 1209 (w), 1176 (m), 1152 (w), 1106 (m), 1040 (w), 1013 (w), 996 (m), 940 (w), 922 (w), 897 (w), 849 (w), 803 (w), 772 (m), 749 (s), 740 (s), 727 (s), 711 (s), 614 (m), 584 (s), 533 (m);

MS (GC, 70 eV) *m/z* (%): 252 (15), 251 (84), 250 (21), 236 (21), 222 (12), 195 (61), 194 (100), 193 (11), 181 (38), 180 (29), 154 (18), 153 (12), 127 (15), 126 (11), 41 (12);

HRMS (EI): calcd. for $C_{16}H_{17}N_3$ ($[M]^+$) 251.14170, found 251.14156.

1-*tert*-butyl-5,6-dimethoxy-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17q):



Starting from compound **16q** (100 mg, 0.26 mmol), the product **17q** was isolated as brown solid (35 mg, 45 %); mp = 263-264 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.7 (s, 9H, $C(CH_3)_3$), 3.9 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 7.0 (s, 1H, CH_{Ar}), 7.1 (s, 1H, CH_{Ar}), 7.3 (s, 1H, CH_{Ar}), 8.0 (s, 1H, CH_{Ar});

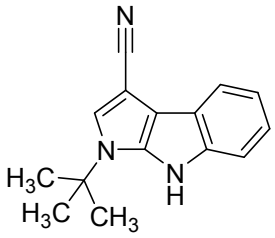
^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.7 ($C(CH_3)_3$), 56.5 (OCH_3), 56.6 (OCH_3), 57.0 ($C(CH_3)_3$), 82.3 (C), 96.6 (CH), 101.7 (CH), 110.2 (C), 113.3 (C), 117.8 (C), 123.9 (CH), 134.0 (C), 136.3 (C), 145.1 (C), 146.4 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3353 (w), 3148 (w), 2966 (w), 2931 (w), 2871 (w), 2832 (w), 2210 (w), 1633 (w), 1577 (m), 1546 (m), 1494 (m), 1467 (s), 1452 (s), 1427 (m), 1411 (m), 1403 (m), 1373 (m), 1342 (w), 1309 (s), 1294 (s), 1247 (m), 1193 (s), 1178 (s), 1163 (s), 1137 (s), 1121 (s), 1093 (m), 1029 (s), 996 (s), 954 (m), 908 (m), 872 (s), 842 (s), 800 (m), 756 (s), 745 (s), 737 (m), 696 (s), 633 (m), 604 (s), 578 (m), 534 (m);

MS (GC, 70 eV) *m/z* (%): 298 ($[M+H]^+$, 17), 297 ($[M]^+$, 89), 242 (14), 241 (100), 240 (26), 227 (13), 226 (92), 198 (11), 183 (11), 170 (10), 154 (10), 57 (11);

HRMS (ESI-TOF): calcd. for $C_{17}H_{19}N_3O_2$ ($[M+H]^+$) 298.1550, found 298.15519.

1-*tert*-butyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17r):



Starting from compound **16r** (100 mg, 0.31 mmol), the product **17r** was isolated as brown solid (52 mg, 70 %); Beige solid, yield 80 %; mp = 142 - 143 °C.

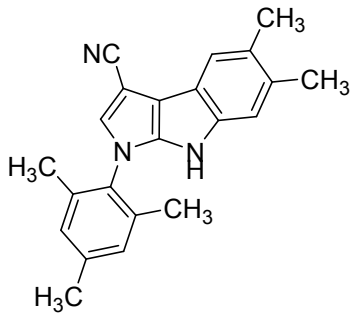
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65 (s, 9H, $C(CH_3)_3$), 7.07-7.16 (m, 3H, CH_{Ar}), 7.33-7.39 (m, 1H, CH_{Ar}), 7.71-7.78 (m, 1H, CH_{Ar}), 9.71 (s, 1H, N*H*). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 29.9, 57.4, 89.7, 109.0, 110.7, 113.7, 116.4, 119.9, 123.7, 128.4, 130.0, 132.6, 142.9;

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3381.1 (s), 3146 (s), 3000.8 (s), 2978.9 (s), 2219.0 (s), 1589.3 (s), 1560.4 (s), 1510 (s), 1487.9 (s), 1450 (s), 1373.1 (s), 1299.1 (s), 1206.6 (s), 1197.6 (s), 1156.9 (s), 1085.2 (s), 1019.2 (s), 823.3, 744.6 (s), 637.4 (s);

MS (GC, 70 eV) *m/z* (%): 237 ([M]$^+$, 35), 182 (13), 181 (100), 180 (26), 154 (14), 127 (11);HRMS (EI): calcd. for $C_{15}H_{15}N_3$ ([M]$^+$) 237.12605, found 237.12604.

1-mesityl-5,6-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (17s):

Starting from 5-amino-1-mesityl-1*H*-pyrrole-3-carbonitrile (100 mg, 0.44 mmol), the product **17s** was isolated as brown solid (65 mg, 82 %); mp = 285-286°C.



^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.00 (s, 6H, CH_3), 2.37 (s, 6H, CH_3), 2.40 (s, 3H, CH_3), 6.96 (s, 1H, CH_{Ar}), 7.02 (s, 2H, CH_{Ar}), 7.08 (s, 1H, CH_{Ar}), 7.42 (s, 1H, N*H*), 7.67 (s, 1H, CH_{Ar});

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4 (CH_3), 20.0 (CH_3), 20.4 (CH_3), 21.1 (CH_3), 85.1 (C), 107.9 (C), 112.5 (CH), 117.1 (C), 119.2 (C), 119.65 (CH), 126.8 (CH), 129.3 (C), 129.4 (CH), 131.1 (C), 132.4 (C), 136.1 (C), 137.8 (C), 138.2 (C), 139.7 (C);

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3257 (w), 3129 (w), 3017 (w), 2918 (w), 2855 (w), 2222 (s), 1633 (w), 1610 (w), 1572 (s), 1553 (s), 1524 (m), 1486 (s), 1457 (s), 1384 (w), 1376 (w), 1324 (m), 1291 (s), 1274 (m), 1244 (w), 1210 (m), 1176 (s), 1115 (m), 1046 (s), 1021 (m), 1004 (m), 954 (w), 856 (m), 845 (s), 803 (m), 749 (s), 736 (m), 714 (m), 686 (m), 664 (w), 636 (m), 586 (m), 547 (s);

MS (GC, 70 eV) *m/z* (%): 328 (25), 327 ([M]$^+$, 100), 326 (33), 312 (28), 275 (15);

HRMS (ESI-TOF): calcd. for $C_{19}H_{14}ClN_3$ ([M+H]$^+$) 328.18082, found 328.18081.

Supplement 2: Crystallographic data

Crystal data and structure refinement for compound **2h**:

Identification Code	is_mc6me234	
Empirical formula	$C_{22}H_{23}NO_5$	
Formula weight	381.41	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group (H.-M.)	P -1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 9.0845(2) Å	α = 93.9180(10)°
	b = 10.1018(2) Å	β = 94.2530(10)°
	c = 11.4606(2) Å	γ = 113.9650(10)°
Volume	952.81(3) $Å^3$	
Z	2	
Calculated density	1.329 mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	404	
Crystal size	0.200 x 0.190 x 0.110 mm	
Θ range for data collection	2.469 to 32.499°	
Index ranges	$-13 \leq h \leq 13$, $-15 \leq k \leq 15$, $-17 \leq l \leq 17$	
Reflections collected	31328	
Independent reflections	6845 [R(int) = 0.0332]	
Absorption correction	Multi-scan	
Max. and min. transmission	0.7464 and 0.7160	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	4687/0/258	
Goodness-of-fit on F^2	1.023	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0455, wR2 = 0.1036	
R indices (all data)	R1 = 0.0778, wR2 = 0.1199	

Crystal data and structure refinement for compound **5c**:

Identification Code	is_mcsr10	
Empirical formula	$C_{27}H_{25}NO_2$	
Formula weight	395.48	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group (H.-M.)	P 21/c	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 11.2788(13) Å	α = 90°
	b = 7.5335(8) Å	β = 100.062(3)°
	c = 25.535(3) Å	γ = 90°
Volume	2136.3(4) $Å^3$	
Z	4	
Calculated density	1.230 mg/m^3	
Absorption coefficient	0.077 mm^{-1}	
F(000)	840	
Crystal size	0.320 x 0.070 x 0.050 mm	
Θ range for data collection	2.651 to 25.042°	
Index ranges	$-13 \leq h \leq 13$, $-8 \leq k \leq 8$, $-30 \leq l \leq 23$	
Reflections collected	16778	
Independent reflections	3756 [R(int) = 0.0822]	
Absorption correction	Multi-scan	
Max. and min. transmission	0.7452 and 0.6558	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	1951/0/274	
Goodness-of-fit on F^2	1.016	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0561, wR2 = 0.1030	
R indices (all data)	R1 = 0.1415, wR2 = 0.1362	

Crystal data and structure refinement for compound **6i**:

Identification Code	is_mcs1tbu	
Empirical formula	$C_{32}H_{35}NO_2$	
Formula weight	465.61	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group (H.-M.)	P -1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 7.7489(2) Å	α = 83.9050(10)°
	b = 12.5424(3) Å	β = 80.8950(10)°
	c = 13.8544(3) Å	γ = 86.0430(10)°
Volume	1320.15(5) $Å^3$	
Z	2	
Calculated density	1.171 mg/m^3	
Absorption coefficient	0.072 mm^{-1}	
F(000)	500	
Crystal size	0.900 x 0.130 x 0.130 mm	
Θ range for data collection	2.321 to 31.000°	
Index ranges	$-11 \leq h \leq 11$, $-18 \leq k \leq 18$, $-20 \leq l \leq 20$	
Reflections collected	41500	
Independent reflections	8425 [R(int) = 0.0271]	
Absorption correction	Multi-scan	
Max. and min. transmission	0.7464 and 0.7145	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	6204/3/351	
Goodness-of-fit on F^2	1.014	
Final R indices [I>2σ(I)]	R1 = 0.0499, wR2 = 0.1274	
R indices (all data)	R1 = 0.0745, wR2 = 0.1463	

Crystal data and structure refinement for compound **10a**:

Identification Code	is_mc_q6m23ome	
Empirical formula	$C_{18}H_{14}F_3NO_2$	
Formula weight	333.30	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group (H.-M.)	P 21/c	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 8.4267(6) Å	α = 90°
	b = 21.8222(13) Å	β= 92.672(4)°
	c = 16.9030(11) Å	γ = 90°
Volume	3104.9(4) $Å^3$	
Z	8	
Calculated density	1.426 mg/m^3	
Absorption coefficient	0.117 mm^{-1}	
F(000)	1376	
Crystal size	0.420 x 0.160 x 0.070 mm	
Θ range for data collection	2.222 to 28.998°	
Index ranges	$-13 \leq h \leq 13$, $-15 \leq k \leq 15$, $-17 \leq l \leq 17$	
Reflections collected	8417	
Independent reflections	7714 [R(int) = 0.0456]	
Absorption correction	Multi-scan	
Max. and min. transmission	0.745979 and 0.703927	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	3625/0/437	
Final R indices [I>2σ(I)]	R1 = 0.0691, wR2 = 0.1091	
R indices (all data)	R1 = 0.1795, wR2 = 0.1307	

Crystal data and structure refinement for compound **11e**:

Identification Code	ah_mc_qme4tbu	
Empirical formula	$C_{23}H_{20}F_3N$	
Formula weight	367.40	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group (H.-M.)	P -1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 8.6097(3) Å	α = 87.457(2)°
	b = 9.9849(3) Å	β = 85.216(2)°
	c = 11.4832(4) Å	γ = 70.471(1)°
Volume	927.00(5) $Å^3$	
Z	2	
Calculated density	1.316 mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	384	
Crystal size	0.280 x 0.200 x 0.100 mm	
Θ range for data collection	2.164 to 32.495°	
Index ranges	$-12 \leq h \leq 12$, $-15 \leq k \leq 14$, $-17 \leq l \leq 17$	
Reflections collected	29319	
Independent reflections	6674 [R(int) = 0.0321]	
Absorption correction	Multi-scan	
Max. and min. transmission	0.7464 and 0.6933	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	5272/0/248	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2σ(I)]	R1 = 0.0431, wR2 = 0.1175	
R indices (all data)	R1 = 0.0566, wR2 = 0.1282	

Crystal data and structure refinement for compound **14e**:

Identification Code	is_mcme4fpr	
Empirical formula	$C_{14}H_{16}F\ N_3O_3S$	
Formula weight	325.36	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group (H.-M.)	P -1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 7.2249(2) Å	α = 114.1390(10)°
	b = 10.8280(2) Å	β = 99.738(2)°
	c = 10.9017(3) Å	γ = 102.4460(10)°
Volume	727.62(3) $Å^3$	
Z	2	
Calculated density	1.485 mg/m^3	
Absorption coefficient	0.250 mm^{-1}	
F(000)	340	
Crystal size	0.260 x 0.100 x 0.090 mm	
Θ range for data collection	3.016 to 31.497°	
Index ranges	$-10 \le h \le 10, -15 \le k \le 15, -16 \le l \le 16$	
Reflections collected	21574	
Independent reflections	4767 [R(int) = 0.0359]	
Absorption correction	Multi-scan	
Max. and min. transmission	0.7463 and 0.7040	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	3468/0/207	
Goodness-of-fit on F^2	1.011	
Final R indices [I>2σ(I)]	R1 = 0.0426, wR2 = 0.0920	
R indices (all data)	R1 = 0.0709, wR2 = 0.1050	

List of abbreviations

Ac	Acetyl
AChE	Acetylcholinesterase
Ar	Aryl
AP	Alkaline Phosphatase
ATR	Attenuated total reflection
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Bu	Butyl
Cy	Cyclohexyl
Cp	Cyclopentyl
DCM	Dichloromethane
DMA	N, N-dimethylacetamide
DMF	N, N-dimethylformamide
DMSO	Dimethylsulphoxide
DPEphos	Bis[(2-diphenylphosphino)phenyl] ether
dppf	1,1′-Bis(diphenylphosphino)ferrocene
DNA	Deoxyribonucleic acid
EA	Ethyl acetate
EI	Electron ionization
ESI	Electron spray ionization
Et	Ethyl
Et_3N	Triethylamine
EWG	Electron withdrawing group
GS	Gas chromatography
h	Hours

HRMS	High-resolution mass spectroscopy
Hz	Herz
IC_{50}	Half-maximal inhibitory concentration
i-Pr	Isopropyl
IR	Infrared
J	Coupling constant
λ	Wavelength
Me	Methyl
MCPBA	*meta*-Chloroperoxybenzoic acid
min	Minutes
mp	Melting point
MS	Mass spectroscopy
n-BuLi	*n*-Butyllithium
NMR	Nuclear magnetic resonance
NPP	Nucleotide pyrophosphatases/phosphodiesterase
Ph	Phenyl
R	Organic moiety
t-Bu	*tert*-Butyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography

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